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E 'USPAT' ENTERED AT 09:40:20 ON 27 OCT 96
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  *                W E L C O M E   T O   T H E                    *
  *          U. S.   P A T E N T   T E X T   F I L E              *
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=> e bazin/in
E#     FILE            FREQUENCY  TERM
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E1     USPAT                1      BAZILOVA NEE SVERINOVA, HEDVIKA/IN
E2     USPAT                1      BAZILOVA, HEDVIKA/IN
E3     USPAT                0 --> BAZIN/IN
E4     USPAT                4      BAZIN, ALAIN/IN
E5     USPAT                1      BAZIN, BERNARD/IN
E6     USPAT                1      BAZIN, CLAUDE/IN
E7     USPAT                1      BAZIN, GEORGE L II/IN
E8     USPAT                1      BAZIN, HERVE/IN
E9     USPAT                7      BAZIN, LUCAS J/IN
E10    USPAT                9      BAZIN, LUCAS JOHN/IN
E11    USPAT                1      BAZIN, MARC/IN
E12    USPAT                2      BAZIN, MICHELLE/IN
=> s e8
L1            1 "BAZIN, HERVE"/IN
=> d l1

1.  4,789,735, Dec. 6, 1988, Conjugate constituted from a wall adhesin of
S. mutans of proteinic nature and from a polysaccharide of S. mutans, its
preparation and its use particularly in anti-caries vaccines; Robert
Frank, et al., 424/197.11, 49, 194.1, 242.1, 244.1; 514/23, 54, 835;
530/395, 402, 403, 405, 806; 536/1.11, 123 [IMAGE AVAILABLE]
=> s lo(w)cd2 or lo(w)cd2a
          9758 LO
           680 CD2
             0 LO(W)CD2
          9758 LO
             3 CD2A
             0 LO(W)CD2A
L2           0 LO(W)CD2 OR LO(W)CD2A
=> s cd2(p)antibod?
           680 CD2
         20873 ANTIBOD?
L3          88 CD2(P)ANTIBOD?
=> s l3(p)(humanis? or humaniz? or chimeric)
            32 HUMANIS?
           207 HUMANIZ?
          1440 CHIMERIC
L4            2 L3(P)(HUMANIS? OR HUMANIZ? OR CHIMERIC)
=> d l4 1-2

1.  5,502,167, Mar. 26, 1996, CDR grafted humanised chimeric T-cell
antibodies; Herman Waldmann, et al., 530/387.3; 435/69.1, 69.7, 91.1,
240.1, 240.2, 240.27, 252.3; 320.1; 530/387.1, 388.22, 388.75, 867;
536/23.53 [IMAGE AVAILABLE]

2.  5,296,353, Mar. 22, 1994, Evaluation and treatment of patients with
progessive immunosuppression; Augusto C. Ochoa, et al., 435/7.23;
424/93.71, 534; 435/7.24, 7.4, 15, 29; 436/63, 64, 86 [IMAGE AVAILABLE]
=> d l4 1-2 kwic
```

US PAT NO: 5,502,167 [IMAGE AVAILABLE] L4: 1 of 2

ABSTRACT:

A **humanised** **antibody** is provided in which the amino acid sequence of the CDRs is derived from the sequence of CDRs of a monoclonal **antibody** having the specificity of binding to resting and activated T-cells, inhibiting T-cell proliferation and lysing T-cells from mice transgenic for human **CD2** and in which sufficient of the amino acid sequence of each CDR has been retained to provide the same specificity for the **humanised** **antibody**.

SUMMARY:

BSUM(1)

The present invention relates to a **humanized** **antibody** which binds to resting and activated T cells, inhibits T cell proliferation and lyses T cells from mice transgenic for human **CD2**, to the preparation of such an **antibody** and to a pharmaceutical composition which contains the **antibody**.

SUMMARY:

BSUM(7)

According to one aspect the present invention provides a **humanised** **antibody** in which the amino acid sequence of the CDRs is derived from the sequence of the CDRs of a monoclonal **antibody** having the specificity of binding to resting and activated T-cells, inhibiting T-cell proliferation and lysing T-cells from mice transgenic for human **CD2** and in which sufficient of the amino acid sequence of each CDR has been retained to provide the same specificity for the **humanised** **antibody**.

SUMMARY:

BSUM(19)

The . . . Nos: 3 to 8 and Seq ID Nos: 11 to 16 respectively are the CDRs of the anti-human T cell **antibody** YTH 655(5)6. YTH 655(5)6 is a rat IgG2b monoclonal **antibody** which binds to resting and activated T cells, inhibits T cell proliferation and lyses T cells from mice transgenic for human **CD2**. The specificity of a **humanized** YTH 655 **antibody** can be determined by its ability to bind to resting and activated T cells, inhibit T cell proliferation and lyse T cells from mice transgenic for human **CD2**.

CLAIMS:

CLMS(1)

We claim:

1. A **humanised** **antibody** that specifically binds resting and activated T-cells, inhibits T-Cell proliferation and lyses T-cells from mice transgenic for human **CD2**, the heavy and light chain variable domains of said **antibody** are composed of framework and complementary

determining regions, wherein light chain complementary determining region 1 has the amino acid sequence. . .

US PAT NO: 5,296,353 [IMAGE AVAILABLE] L4: 2 of 2

DETDESC:

DETD(10)

The **antibody** to a T lymphocyte surface receptor can be made by well known and conventional methods, for example those described in. . . A. M. Jruisbeek, D. H. Margulies, E. M. Shevach and W. Strober (eds.), Green Publishing Associates and Wiley-Interscience, 2.4.1-2.10.3 (1991). **Antibodies** to a surface receptor that can be used alone, or in combination with other **antibodies** to different T cell surface receptors, in a method for the activation of T lymphocytes, include, but are not limited to, anti-**CD2**, anti-CD3, anti-CD4, anti-CD5, anti-CD6, anti-CD7, anti-CD8, anti-CD28, anti-CDw29, or anti-CD45R. It is preferably an anti-CD3 MAb. The anti-CD3 MAb can. . . about 10 ng/ml, or less, anti-CD3 MAb. Mouse anti-human OKT3 is available from the Ortho Division of Johnson and Johnson. **Humanized** versions of the **antibodies** will have utility for T cell activation in vivo during treatment.

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=> d his
     (FILE 'USPAT' ENTERED AT 09:40:20 ON 27 OCT 96)
                E BAZIN/IN
L1            1 S E8
L2            0 S LO(W)CD2 OR LO(W)CD2A
L3           88 S CD2(P)ANTIBOD?
L4            2 S L3(P)(HUMANIS? OR HUMANIZ? OR CHIMERIC)
=> s l3 and (humaniz? or humanis? or chimeric)
          207 HUMANIZ?
           32 HUMANIS?
         1440 CHIMERIC
L5          23 L3 AND (HUMANIZ? OR HUMANIS? OR CHIMERIC)
=> d l5 1-23
```

1. 5,567,805, Oct. 22, 1996, The cellular receptor for the CS3 peptide of human immunodeficiency virus; Lee A. Henderson, et al., 530/350; 435/5; 530/326 [IMAGE AVAILABLE]

2. 5,556,763, Sep. 17, 1996, Evaluation and treatment of patients with progressive immunosuppression; Augusto C. Ochoa, et al., 435/7.23; 424/9.2, 93.71; 435/6, 7.24; 436/501 [IMAGE AVAILABLE]

3. 5,545,405, Aug. 13, 1996, Method for treating a mammal suffering from cancer with a cho-glycosylated antibody; Martin J. Page, 424/133.1, 130.1, 143.1, 172.1, 174.1; 435/70.3, 71.1, 240.1, 320.1; 530/387.1, 388.1, 388.22, 388.73, 388.75, 389.1, 389.6, 389.7 [IMAGE AVAILABLE]

4. 5,545,404, Aug. 13, 1996, Method for treating a mammal suffering from a T-cell medicated disorder with a CHO-Glycosylated antibody; Martin J. Page, 424/133.1, 130.1, 143.1, 173.1, 174.1; 435/70.3, 71.1, 240.1, 320.1; 530/387.1, 388.22, 388.73, 388.75, 388.8, 389.1, 389.6, 389.7 [IMAGE AVAILABLE]

5. 5,545,403, Aug. 13, 1996, Method for treating a mammal by administering a CHO-glycosylated antibody; Martin J. Page, 424/133.1,

130.1, 135.1, 136.1, 138.1, 143.1, 147.1, 150.1, 159.1, 172.1, 174.1; 435/70.3, 71.1, 240.1, 320.1; 530/387.1, 388.1, 388.22, 388.73, 388.75, 389.1, 389.6, 389.7 [IMAGE AVAILABLE]

6. 5,529,932, Jun. 25, 1996, Isolated DNA encoding a plant ribosome inactivating protein from the leaves of saponaria officinalis; Rolando Lorenzetti, et al., 435/320.1, 69.1, 172.3, 252.33; 536/23.6 [IMAGE AVAILABLE]

7. 5,525,461, Jun. 11, 1996, Therapeutic and diagnostic methods using total leukocyte surface antigens; Charles W. Rittershaus, 435/5, 7.1, 7.2, 7.21, 7.22, 7.23, 7.24, 7.92, 7.93, 7.94, 7.95, 974, 975 [IMAGE AVAILABLE]

8. 5,521,288, May 28, 1996, CD28IG fusion protein; Peter S. Linsley, et al., 530/387.3; 435/7.2, 7.92, 69.1, 69.7, 91.1, 240.1, 252.3, 252.33, 320.1; 530/300, 350, 387.1, 395, 409, 866, 867, 868; 536/23.1, 23.4, 23.53 [IMAGE AVAILABLE]

9. 5,510,461, Apr. 23, 1996, pp: A newly identified CD45-associated protein; Stefan Meuer, et al., 530/350; 435/6; 530/387.9 [IMAGE AVAILABLE]

10. 5,506,126, Apr. 9, 1996, Rapid immunoselection cloning method; Brian Seed, et al., 435/172.3, 320.1; 536/24.2 [IMAGE AVAILABLE]

11. 5,502,167, Mar. 26, 1996, CDR grafted **humanised** **chimeric** T-cell antibodies; Herman Waldmann, et al., 530/387.3; 435/69.1, 69.7, 91.1, 240.1, 240.2, 240.27, 252.3, 320.1; 530/387.1, 388.22, 388.75, 867; 536/23.53 [IMAGE AVAILABLE]

12. 5,439,665, Aug. 8, 1995, Detection and treatment of infectious and inflammatory lesions; Hans J. Hansen, et al., 424/1.49, 153.1, 154.1, 172.1, 173.1; 530/391.3 [IMAGE AVAILABLE]

13. 5,426,029, Jun. 20, 1995, Therapeutic and diagnostic methods using leukocyte surface antigens; Charles W. Rittershaus, et al., 435/7.21, 7.24, 7.9, 7.94; 436/501, 506, 518, 536 [IMAGE AVAILABLE]

14. 5,411,861, May 2, 1995, Rapid mutational analysis method; Brian Seed, et al., 435/6, 7.1, 69.1, 91.4, 172.3, 270; 530/388.2 [IMAGE AVAILABLE]

15. 5,364,612, Nov. 15, 1994, Detection of cardiovascular lesions; David M. Goldenberg, 424/1.53, 1.49, 9.341, 136.1, 152.1, 153.1, 154.1, 172.1, 173.1; 530/391.3 [IMAGE AVAILABLE]

16. 5,296,353, Mar. 22, 1994, Evaluation and treatment of patients with progessive immunosuppression; Augusto C. Ochoa, et al., 435/7.23; 424/93.71, 534; 435/7.24, 7.4, 15, 29; 436/63, 64, 86 [IMAGE AVAILABLE]

17. 5,292,636, Mar. 8, 1994, Therapeutic and diagnostic methods using soluble T cell surface molecules; Patrick C. Kung, et al., 435/5, 7.23, 7.24, 7.9, 7.94, 34, 974, 975; 436/506, 518, 536, 548, 811, 813 [IMAGE AVAILABLE]

18. 5,225,540, Jul. 6, 1993, Monoclonal antibodies to tissue plasminogen activator (T-PA) which prolong its functional half-life; Thomas M.

Reilly, et al., 530/388.25; 424/145.1, 146.1; 435/70.21, 172.2, 240.27; 530/388.26, 389.3; 935/104, 107 [IMAGE AVAILABLE]

19. 5,185,250, Feb. 9, 1993, Human .gamma., .delta.T cell antigen receptor polypeptides and nucleic acids; Michael B. Brenner, et al., 435/69.3, 7.24, 69.1, 172.2, 240.27; 530/350, 387.9, 388.22, 388.75; 536/23.5 [IMAGE AVAILABLE]

20. 5,165,923, Nov. 24, 1992, Methods and compositions for the treatment of Hodgkin's disease; Philip Thorpe, et al., 424/179.1, 153.1, 154.1, 178.1; 530/388.7, 388.73, 388.75, 391.9 [IMAGE AVAILABLE]

21. 5,124,251, Jun. 23, 1992, CD3 .zeta. co-associated complex on CD16.sup.- NK cells; Lewis L. Lanier, et al., 435/7.21, 7.24; 436/547, 548 [IMAGE AVAILABLE]

22. 5,104,652, Apr. 14, 1992, Compositions and method for treatment of cancer using monoclonal antibody against G.sub.D3 ganglioside together with IL-2; Alan N. Houghton, et al., 424/85.2, 85.1, 137.1, 156.1, 809; 435/240.2, 240.21, 240.25; 530/387.5, 388.73, 388.75, 388.85, 864 [IMAGE AVAILABLE]

23. 4,925,648, May 15, 1990, Detection and treatment of infectious and inflammatory lesions; Hans J. Hansen, et al., 424/1.53; 252/1; 424/9.34, 136.1, 153.1, 154.1, 178.1; 530/388.7, 388.73, 388.75, 389.6, 391.3, 402, 866 [IMAGE AVAILABLE]
=> d l5 1-20 kwic

US PAT NO: 5,567,805 [IMAGE AVAILABLE] L5: 1 of 23

DETDESC:

DETD(20)

The monoclonal antibodies for therapeutic use may be human monoclonal antibodies or **chimeric** human-mouse (or other species) monoclonal antibodies. Human monoclonal antibodies may be made by any of numerous techniques known in the. . . Proc. Natl. Acad. Sci. U.S.A. 80:7308-7312; Kozbor et al., 1983, Immunology Today 4:72-79; Olsson et al., 1982, Meth. Enzymol. 92:3-16). **Chimeric** antibody molecules may be prepared containing a mouse antigen-binding domain with human constant regions (Morrison et al., 1984, Proc. Natl.. . .

DETDESC:

DETD(39)

C-CS3-HSA-FITC . . . were also positive by flow cytometry. PBMC subset analysis was performed by dual staining with C-CS3-HSA-Rho and fluorescein labelled monoclonal **antibodies** (Coulter Cytometry) to CD4, CD8, **CD2** for T cells (T4, T8 and T11, respectively), HLA-DR for B (I2) and CD11b or CD14 for monocytes (MO1 and MO2, respectively). Analysis revealed 90% of **CD2**, CD4 or DR cells were CS3 positive, 87% of MO1 or MO2 cells were CS3 positive and 60% of CD8. . .

DETDESC:

DETD(90)

Further analysis was performed with monoclonals to T cells (**antibodies** to CD4, CD8, and **CD2**, Coulter), B cells (B4, Coulter), and monocytes (MO1 and MO2, Coulter) in double staining with CS3-HSA. Rhodamine showed that lymphocytes. . .

DETDESC:

DETD(94)

. . .
II

EXPRESSION OF CS3 RECEPTOR ON PERIPHERAL BLOOD MONONUCLEAR CELLS

Cell Subset	% Expressing CS3 Receptor
CD4	90*
CD2	90
HLA-DR	90
MO1	87
MO2	87
CD8	60

*Dual fluorescence flow cytometry was used to determine the percentage of each subset positive for expression of CS3, using CS3HSA-Rhodamine or FITC. Subset markers were monoclonal **antibodies** from Coulter as follows: cells, T4 for helper, T8 for suppressor cytotoxic, T11 for pan T cells, 1 for. . .

US PAT NO: 5,556,763 [IMAGE AVAILABLE] L5: 2 of 23

SUMMARY:

BSUM(15)

The . . . couple stimulation of the receptor with the signal transduction pathways. B. A. Irving et al., Cell, 64:891 (1991). When a **chimeric** protein linking the extracellular and transmembrane domains of CD8 to the cytoplasmic domain of the .zeta. chain was constructed, the **chimeric** protein activated the appropriate signal transduction pathways in the absence of CD3.gamma., .delta., and .epsilon.. Therefore the role of .zeta.. . .

DETDESC:

DETD(17)

A . . . these LGLs do have lytic function. Thus, target cell lysis is not dependent on the presence of the CD3.zeta.-chain. Moreover, **chimeric** molecules made with Fc.epsilon..gamma. expressed in cytotoxic T cell lines maintain their lytic function. This suggests that Fc.epsilon..gamma. and .zeta.. . .

DETDESC:

DETD(223)

Antibodies to a surface receptor are used alone, or in combination with other **antibodies** to different T cell surface receptors to activate T lymphocytes. Suitable **antibodies** include anti-**CD2**, anti-CD3, anti-CD4, anti-CD5, anti-CD6, anti-CD7, anti-CD8, anti-CD28, anti-CDw29, and anti-CD45R. A preferred **antibody** is anti-CD3 monoclonal **antibody** (MAb). An anti-CD3 MAb includes OKT3, WT32, Leu-4, SPV-T3c, RIV9, 64.1, 145-2C11, and the like. More preferably, the anti-CD3 MAb. . . Type Culture Collection (ATCC). Mouse anti-human OKT3 is available from the Ortho Division of Johnson and Johnson. Versions of the **antibodies** derived from humans are useful for T cell activation in vivo during treatment. T lymphocytes treated with anti-CD3 MAb for. . .

US PAT NO: 5,545,405 [IMAGE AVAILABLE] L5: 3 of 23

SUMMARY:

BSUM(9)

When, . . . problem has therefore been addressed by the development of antibodies of two basic types. The first type, referred to as **chimeric** antibodies, is where the murine constant domains only are replaced by equivalent domains of human origin (Morrison et al, P.N.A.S.,. . . all replaced by equivalent domains and regions of human origin. This second type of antibody is referred to as a **humanised** or CDR-grafted antibody (Jones et al, Nature, 1986, 321, 522-525; and Riechmann et al, Nature, 1988, 332, 323-327). A human antibody would of course avoid the need for "**humanisation**", however cell lines which secrete human antibodies are very unstable and have generally proven unsuitable for commercial scale production.

SUMMARY:

BSUM(15)

The . . . more further modifications to improve antigen binding ability or to alter effector functioning. Another form of altered antibody is a **humanised** or CDR-grafted antibody including a composite antibody, wherein parts of the hypervariable regions in addiron to the CDRs are transferred. . .

SUMMARY:

BSUM(16)

The cell line of the invention is preferentially employed for the production of altered **antibodies** most preferably chimaeric **antibodies** or CDR-grafted **antibodies**. Particular examples of these include **antibodies** against T cell markers such as **CD2**, CD3, CD4, CD5, CD7, CD8, CD11a, CD11b, CD18, CD19, CD25, CD45 and CDw52 and especially CDR grafted **antibodies** against the CDw52 antigen, such as Campath-1H (Campath is a Trademark of the Wellcome Foundation Ltd) described in EP 328404 Further examples include CDR-grafted **antibodies** against various cancer cell marker antigens such as CD33 and CD38.

DETDESC:

DETD(53)
EXPRESSION OF **HUMANISED** ANTI-CD4 ANTIBODY FROM CHO CELLS

DETDESC:

DETD(56)

The cDNA encoding the **humanised** CD4 light chain was cloned into pLD9 [Page and Sydenham, M. A. 199 Biotechnology 9 64-68]. The resulting plasmid was designated p2110. The **humanised** CD4 heavy chain was sequenced and cloned into a modified version of plasmid p342-12 (Law M-F., Byrne, J. C. and. . .

DETDESC:

DETD(57)

Plasmid . . . neomycin resistance gene, the .beta.-lactamase gene and the .beta.-actin expression cassette containing the unique HinDIII site. The cDNA encoding the **humanised** heavy chain was cloned into this site and the resulting plasmid containing the correctly orientated insert was designated pBanCD4H. Thus,. . .

CLAIMS:

CLMS(1)

I . . .

method for treating a human suffering from cancer by administering a therapeutically effective amount of a whole glycosylated recombinant human, **chimeric**, CDR grafted or bispecific antibody effective in treating said cancer, wherein the improvement comprises an antibody glycosylated by a Chinese. . .

US PAT NO: 5,545,404 [IMAGE AVAILABLE] L5: 4 of 23

SUMMARY:

BSUM(8)

When, . . . problem has therefore been addressed by the development of antibodies of two basic types. The first type, referred to as **chimeric** antibodies, is where the murine constant domains only are replaced by equivalent domains of human origin (Morrison et al, P.N.A.S.,. . . all replaced by equivalent domains and regions of human origin. This second type of antibody is referred to as a **humanised** or CDR-grafted antibody (Jones et al, Nature, 1986, 321, 522-525; and Riechmann et al, Nature, 1988, 332, 323-327). A human antibody would of course avoid the need for "**humanisation**", however cell lines which secrete human antibodies are very unstable and have generally proven unsuitable for commercial scale production.

SUMMARY:

BSUM(14)

The . . . more further modifications to improve antigen binding ability or to alter effector functioning. Another form of altered antibody is a **humanised** or CDR-grafted antibody including a composite antibody, wherein parts of the hypervariable regions in additon to the CDRs are transferred. . .

SUMMARY:

BSUM(15)

The cell line of the invention is preferentially employed for the production of altered **antibodies** most preferably chimaeric **antibodies** or CDR-grafted **antibodies**. Particular examples of these include **antibodies** against T cell markers such as **CD2**, CD3, CD4, CD5, CD7, CD8, CD11a, CD11b, CD18, CD19, CD25, CD45 and CDw52 and especially CDR grafted **antibodies** against the CDw52 antigen, such as Campath-1H (Campath is a Trademark of the Wellcome Foundation Ltd) described in EP 328404 Further examples include CDR-grafted **antibodies** against various cancer cell marker antigens such as CD33 and CD38.

DETDESC:

DETD(54)
EXPRESSION OF **HUMANISED** ANTI-CD4 ANTIBODY FROM CHO CELLS

DETDESC:

DETD(57)

The cDNA encoding the **humanised** CD4 light chain was cloned into pLD9 [Page and Sydenham, M. A. 1991 Biotechnology 9 64-68]. The resulting plasmid was designated p2110. The **humanised** CD4 heavy chain was sequenced and cloned into a modified version of plasmid p342-12 [Law M-F., Byrne, J. C. and. . .

DETDESC:

DETD(58)

Plasmid . . . neomycin resistance gene, the .beta.-lactamase gene and the .beta.-actin expression cassette containing the unique HinDIII site. The cDNA encoding the **humanised** heavy chain was cloned into this site and the resulting plasmid containing the correctly orientated insert was designated pBanCD4H. Thus,. . .

CLAIMS:

CLMS(1)

I . . .

a human suffering from a T-cell mediated disorder comprising administering a therapeutically effective amount of a whole glycosylated recombinant human, **chimeric**, CDR-grafted or bispecific antibody effective in treating said disorder, wherein the improvement comprises an antibody glycosylated by a Chinese hamster. . .

US PAT NO: 5,545,403 [IMAGE AVAILABLE] L5: 5 of 23

SUMMARY:

BSUM(8)

When, . . . problem has therefore been addressed by the development of antibodies of two basic types. The first type, referred to as **chimeric** antibodies, is where the murine constant domains only are replaced by equivalent domains of human origin (Morrison et al, P.N.A.S.,. . . all replaced by equivalent domains and regions of human origin. This second type of antibody is referred to as a **humanised** or CDR-grafted antibody (Jones et al, Nature, 1986, 321, 522-525; and Riechmann et al, Nature, 1988, 332, 323-327). A human antibody would of course avoid the need for "**humanisation**", however cell lines which secrete human antibodies are very unstable and have generally proven unsuitable for commercial scale production.

SUMMARY:

BSUM(12)

The . . . more further modifications to improve antigen binding ability or to alter effector functioning. Another form of altered antibody is a **humanised** or CDR-grafted antibody including a composite antibody, wherein parts of the hypervariable regions in addition to the CDRs are transferred. . .

SUMMARY:

BSUM(13)

The cell line of the invention is preferentially employed for the production of altered **antibodies** most preferably chimaeric **antibodies** or CDR-grafted **antibodies**. Particular examples of these include **antibodies** against T cell markers such as **CD2**, CD3, CD4, CD5, CD7, CD8, CD11a, CD11b, CD18, CD19, CD25, CD45 and CDw52 and especially CDR grafted **antibodies** against the CDw52 antigen, such as Campath-1H (Campath is a Trademark of the Wellcome Foundation Ltd) described in EP 328404 Further examples include CDR-grafted **antibodies** against various cancer cell marker antigens such as CD33 and CD38.

DETDESC:

DETD(53)
Expression of **Humanised** Anti-CD4 Antibody from CHO Cells

DETDESC:

DETD(55)

The . . . were grafted onto human heavy and light chain frameworks (Winter et al, Nature, 1988, 325 323-327). The cDNA encoding the **humanised** CD4 light chain was cloned into pLD9 [Page and Sydenham, M.A. 1991 Biotechnology 9 64-68]. The resulting plasmid was designated p2110. The **humanised** CD4 heavy chain was sequenced and cloned into a

modified version of plasmid p342-12 [Law M-F., Byrne, J. C. and. . .

DETDESC:

DETD(56)

Plasmid . . . neomycin resistance gene, the .beta.-lactamase gene and the .beta.-actin expression cassette containing the unique HinDIII site. The cDNA encoding the **humanised** heavy chain was cloned into this site and the resulting plasmid containing the correctly orientated insert was designated pBanCD4H. Thus,. . .

CLAIMS:

CLMS(1)

I . . .

a human suffering from a disease or disorder comprising administering a therapeutically effective amount of a whole glycosylated recombinant human **chimeric** or CDR-grafted or bispecific antibody effective in treating said disease or disorder in said human, wherein the improvement comprises an. . .

CLAIMS:

CLMS(6)

6. The method of claim 2, wherein said antibody is a **chimeric** antibody.

CLAIMS:

CLMS(7)

7. The method of claim 3, wherein said antibody is a **chimeric** antibody.

US PAT NO: 5,529,932 [IMAGE AVAILABLE] L5: 6 of 23

SUMMARY:

BSUM(4)

Siena et al (1987) synthesised five immunotoxins by conjugating SO-6 to monoclonal **antibodies** that detected **CD2**, CD3 and CD5 T cell antigens, respectively. These immunotoxins bound to peripheral blood lymphocytes (PBL) and inhibited protein synthesis in. . . at 37.degree. C., mitogen-induced protein synthesis and cell proliferation was inhibited in a dose related manner, while unconjugated SO-6 or **antibodies** alone were not cytotoxic. Cytotoxicity was blocked by preincubation with unconjugated anti- CD5 but not with an irrelevant **antibody**, thus demonstrating that it was caused by specific binding to CD5+cells.

SUMMARY:

BSUM(5)

Recombinant . . . al (1986) who fused the genes coding for a truncated diphtheria toxin fragment and for melanocyte-stimulating hormone (alpha-MSH). The toxin-hormone **chimeric** gene direct the expression of a fused protein that retained the ADP-ribosyltransferase activity and lipid-associating domains of diphtheria toxin. However, the diphtheria toxin receptor-binding domain was replaced with MSH sequences. The **chimeric** toxin was found to be toxic for MSH receptor-positive human malignant melanoma cells in culture, while not being toxic for. . .

SUMMARY:

BSUM(6)

More . . . the gene encoding interleukin-2 (IL-2) to a truncated diphtheria toxin gene also results in the expression of a biologically active **chimeric** IL-2 toxin. The fused protein was shown to be selectively targeted to activated or to malignant T cells carrying specific. . .

US PAT NO: 5,525,461 [IMAGE AVAILABLE] L5: 7 of 23

SUMMARY:

BSUM(7)

TABLE I

LEUKOCYTE SURFACE MOLECULES			
Cell Surface Marker	Expression	Detection Monoclonal **Antibodies**	Refer-ences
T cell Antigen Receptor	All T cells and T cell subsets. . .	T40/25, NAI/34	1, 2, 3, 4, Thymocytes & OKT6
	Langerhans Calls, Lukemia Cells		
NK cell receptor	NK cells	NC-37 specific **antibodies**	7
Cell Adhesion Molecules			
CD2	All T cells	OKT11 Leu5 B67.1	8, 9, 10
CD58 (LFA-3)	Leukocytes, epithelial	TS2/9	11

CD3. . . 206:347-349.
13 Reinherz et al., 1979, Proc. Natl. Acad Sci. USA 76:4061-4065.
14 Ledbetter et al., 1981, Monoclonal **Antibodies** and Tcell Hybridoma,
Elsevier, North Holland, N.Y. pp 16-22.
14a Shieu, L., et al., 1988, J. Exp. Med.. . .

DETDESC:

DETD(23)

Monoclonal . . . and Cancer Therapy, Alan R. Liss, pp. 77-96). In fact, according to the invention, techniques developed for the production of "**chimeric** antibodies" (Morrison et al., 1984, Proc. Nat'l. Acad. Sci. U.S.A. 81:6851- 6855; Neuberger et al., 1984, Nature 312:604-608; Takeda et. . .

DETDESC:

DETD(113)

Experiment . . . Samples with low CD4 positive cell counts were selected from HIV positive specimens. Cells were dually stained with anti-CD4 and anti-**CD2** **antibodies** in order to make sure that the cells counted by Flow were CD4 positive T cells. A total of 95 samples (46 normal and 49 abnormal) were assayed for white blood cell number, lymphocyte differential, and percent **CD2**.sup.+ CD4.sup.+ cells by flow cytometry and for the amount of CD4 by the total CD4 antigen method. The number of. . .

US PAT NO: 5,521,288 [IMAGE AVAILABLE] L5: 8 of 23

SUMMARY:

BSUM(18)

A . . . cells. The method for reacting a ligand for CD28 with T cells may additionally include the use of anti-CD monoclonal **antibodies** such as anti-**CD2** and/or anti-CD3 monoclonal **antibody**.

DETDESC:

DETD(122)

The . . . transcriptase (from Avian myeloblastosis virus; Life Sciences Associates, Bayport, N.Y.)-PCR reaction using RNA from a myeloma cell line producing human-mouse **chimeric** mAb L6 (provided by Dr. P. Fell and M. Gayle, Bristol-Myers Squibb Pharmaceutical Research Institute, Seattle, Wash.) as template. The. . .

DETDESC:

DETD(129)

Immunostaining . . . 10:247 (1980)) or BB-1 (Yokochi et al., supra) at 10 .mu.g/ml, or with Ig fusion proteins (CD28Ig, B7Ig, CD5Ig or **chimeric** mAb L6 containing Ig C.gamma.1, all at 10 .mu.g/ml in DMEM containing 10% FCS) for 1-2 h at 4.degree. C.. . .

DETDESC:

DETD(136)

Binding . . . B7.sup.+ CHO (FIG. 11), suggesting that this molecule

has a tendency to form homophilic interactions. No binding was detected of **chimeric** mAb L6 containing human Ig C.gamma.1, or another fusion protein, CD5Ig. Thus B7Ig and CD28Ig retain binding activity for their. . .

DETDESC:

DETD(140)

Binding . . . the presence or absence of competitor to a concentration of 24 nM in the presence of the concentrations of unlabeled **chimeric** L6 mAb, mAb 9.3, mAb BB-1 or B7Ig, as indicated in FIG. 12. After incubation for 2-3 h at 23.degree.. . .

DETDESC:

DETD(149)

Cell . . . (lane 1), addition of mAb 9.3 (5 .mu.g, lane 2), addition of B7Ig (10 .mu.g, lane 3), or addition of **chimeric** L6 mAb (10 .mu.g, lane 7).

DETDESC:

DETD(150)

As . . . the latter form being more prominent. The protein having a M.sub.r of approximately 45,000 found in the sample precipitated with **chimeric** mAb L6 was due to spillover and was not observed in other experiments. mAb 9.3 was more effective at immunoprecipitation. . .

US PAT NO: 5,510,461 [IMAGE AVAILABLE] L5: 9 of 23

SUMMARY:

BSUM(4)

Resting T lymphocytes can be activated in vitro by monoclonal **antibodies** against the T cell receptor complex (TCR-CD3) or against **CD2**, a 50kD glycoprotein. Activation of resting T lymphocytes by means of monoclonal **antibodies** leads to proliferation and differentiation and therefore mimics the action of the naturally occurring ligands for those receptors (antigen for the T cell receptor or the LFA-3 for **CD2**). The earliest step of T cell activation by either monoclonal **antibodies** or the natural ligands is a phosphorylation of a limited number of intracellular and transmembrane proteins (e.g. CD3 epsilon, CD3. . . Phosphorylation of proteins is thought to be mediated by intracellular protein kinases which are activated upon the binding of monoclonal **antibodies** or the appropriate ligands and which phosphorylate proteins either on tyrosine residues (protein tyrosine kinases) or on threonine- and/or serine. . .

SUMMARY:

BSUM(9)

Using . . . 4.0 to 4.5. In resting T cells, this protein, "pp32", is constitutively phosphorylated on serine. Immunoprecipitation experiments

with anti-CD45 monoclonal **antibodies** have shown that pp32 is specifically associated with CD45. Besides pp32, a tyrosine kinase coprecipitates with the CD45 molecule. The. . . the activation of T lymphocytes. The changes take place within 5 minutes after stimulation of resting T lymphocytes with monoclonaI **antibodies** specific for **CD2** or with Phorbol esters.

DETDESC:

DETD(30)

The . . . the protein to associate with CD45. For example, a variant of pp32 may have altered glycosylation or may be a **chimeric** protein of pp32 and another protein. Additionally, immunogenic portions of pp32 proteins are within the scope of the invention. An. . .

DETDESC:

DETD(35)

Chimeric and **humanized** antibodies are also within the scope of the invention. It is expected that **chimeric** and **humanized** antibodies would be less immunogenic in a human subject than the corresponding non-**chimeric** antibody. A variety of approaches for making **chimeric** antibodies, comprising for example a non-human variable region and a human constant region, have been described. See, for example, Morrison. . . 4,816,397; Tanaguchi et al., European Patent Publication EP 171496; European Patent Publication 0173494, United Kingdom Patent GB 2177096B. Additonally, a **chimeric** antibody can be further "**humanized**" such that parts of the variable regions, especially the conserved framework regions of the antigen-binding domain, are of human origin. . . Meth. Enzymol., 92, 3-16 (1982)), and are preferably made according to the teachings of PCT Publication WO92/06193 or EP 0239400. **Humanized** antibodies can be commercially produced by, for example, Scotgen Limited, 2 Holly Road, Twickenham, Middlesex, Great Britain.

DETDESC:

DETD(39)

The . . . A. in Teratocarcinomas and Embryonic Stem Cells. A Practical Approach, E. J. Robertson, ed. (IRL, Oxford, 1987) pp. 113-152). A **chimeric** embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term. Progeny harbouring. . .

US PAT NO: 5,506,126 [IMAGE AVAILABLE] L5: 10 of 23

SUMMARY:

BSUM(10)

In . . . regulator T cells containing helper and suppressor T lymphocytes. These two subpopulations have been defined with heteroantisera, autoantibodies, and monoclonal **antibodies** directed at cell surface antigens. For example, earlier in their development, human lymphoid cells in the thymus express an antigen designated T11 which

reacts strongly to a monoclonal **antibody** designated Cluster of Differentiation 2 (**CD2**), and react slightly with monoclonal **antibody** CD5 to cell surface antigen T1. During maturation, these cells lose T11 (**CD2**) and acquire three new antigens defined by monoclonal **antibodies** CD4, CD8, and CD1. With further maturation, the thymocytes cease to express cell surface antigens reactive with monoclonal **antibody** CD1, express the T3 antigen reactive with monoclonal **antibody** CD3, and then segregate into two subpopulations which express either T4 (CD4) or T8 (CD5) antigen. Immunologic competence is acquired. . .

SUMMARY:

BSUM(12)

For example, **CD2**, the human T cell erythrocyte receptor, allows thymocytes and T-lymphocytes to adhere to target cells (e.g., erythrocytes) and to thymic epithelium. This occurs via a specific molecular ligand for **CD2**, designated LFA-3, in humans, which is a widely distributed surface antigen. This phenomenon has long been employed to detect, assay and purify human cells producing **antibodies** to sheep erythrocytes and serves as the basis for the E-rosette test, first described by Zaalberg, Nature 202:1231 (1964). **CD2**/LFA-3 interactions also have been shown to mediate cytolytic target conjugation (Shaw et al., Nature 323:262-264 (1986), and the mixed lymphocyte reaction (Martin et al., J. Immunol. 131:180-185 (1983). Anti-**CD2** monoclonal **antibodies** can directly activate peripheral T-lymphocytes via an antigen-independent pathway (Meuer et al., Cell 36:897-906 (1984)), indicating an even wider immunoregulatory role for **CD2**.

SUMMARY:

BSUM(26)

This . . . this invention, a cDNA expression vector comprises a suppressor tRNA gene; an SV40 origin; a synthetic transcription unit, comprising a **chimeric** promoter composed of human cytomegalovirus AD169 immediate early enhancer sequence fused to the HIV LTR -60 to +80 sequences, inserted. . .

SUMMARY:

BSUM(27)

A further aspect of the present invention comprises a synthetic transcription unit for use in a cDNA expression vector, comprising a **chimeric** promoter composed of human cytomegalovirus AD169 immediate early enhancer sequences fused to HIV LTR -60 to +80 sequences. The small. . .

SUMMARY:

BSUM(32)

The immunoselection technique of the present invention allows efficient use of **antibodies**, which may be monoclonal or polyclonal, in relatively small absolute amounts. The method of the present invention also is quite. . . been employed to successfully clone genes encoding

cell surface antigens associated with mammalian T lymphocytes (e.g. antigens CD1a, CD1b, CD1c, **CD2**, CD6, CD7, CD13, CD14, CD16, CD19, CD20, CD22, CD26, CD27, CD28, CD31, CDw32a, CDw32b, CD33, CD34, CD36, CD37, CD38, CD39,. . .

DRAWING DESC:

DRWD(13)

There . . . from the pBR322 origin of replication, 588-1182 from the M13 origin, 1183-1384 from the supF gene, 1385-2238 are from the **chimeric** cytomegalovirus/human immunodeficiency virus promoter, 2239-2647 are from the replaceable fragment, 2648-3547 from plasmid pSV2 (splice and polyadenylation signals), and 3548-3900. . .

DETDESC:

DETD(60)

Vectors . . . may contain a naturally derived or synthetic transcription origin, and the SV40 early region promoter. Even more preferred is a **chimeric** promoter composed of human cytomegalovirus immediate early enhancer sequences. Various "enhancer sequences" also may be used with SV40 vectors. These. . .

DETDESC:

DETD(79)

A . . . inserting a synthetic transcription unit between the suppressor tRNA gene and the SV40 origin. The transcription unit consisted of a **chimeric** promoter composed of human cytomegalovirus AD169 immediately early enhancer sequences fused to the HIV LTR -67 to +80 sequences. Immediately. . .

DETDESC:

DETD(95)

A cDNA encoding **CD2** antigen determinants was isolated in the following manner: cDNA was prepared from RNA extracted from the human T Cell tumor. . . protoplast fusion. Three days later the cells were detached by exposure to EDTA and treated with a pool of monoclonal **antibodies**, including three (OKT11, Leu5b, and Coulter T11) directed against **CD2** determinants. The **antibody**-treated cells were distributed into dishes coated with an affinity purified sheep anti-mouse IgG **antibody**, allowed to attach, and separated from the nonadherent cells by gentle washing. This method of enrichment is known in the. . .

DETDESC:

DETD(96)

The . . . as before. In the third round, a portion of the detached cells was treated with a mixture of three monoclonal **antibodies** specific for **CD2**, and a Hirt supernatant was again generated and transformed into E. coli. DNA was prepared from eight of the resulting colonies and transfected into COS cells. After three days, surface

expression of the **CD2** antigen was detected by indirect immunofluorescence in six of eight transfected dishes. Restriction enzyme digestion of the corresponding plasmid DNAs. . .

DETDESC:

DETD(107)

COS cells were transfected with the **CD2** expression plasmid and surface labeled with 125.sub.I by the lactoperoxidase method 60 hours post-transfection. A cell lysate was prepared, and portions were incubated either with monoclonal anti-**CD2** **antibody** (OKT11) or with an extraneous (OKT4; anti-CD4) **antibody** for 2 hours at 4.degree. C. Sepharose-bound anti-mouse **antibody** was added, and after several washing steps, the adsorbed proteins were eluted and electrophoresed through a 11.25% acrylamide gel together. . . line generated in this laboratory. Autoradiography demonstrated a prominent band of immunoreactive material precipitated from transfected COS cells by the anti-**CD2** **antibody**, but not by the control. The calculated mean molecular weight of the COS cell material was 51 kd, compared to. . .

DETDESC:

DETD(109)

COS cells transfected with the **CD2** expression clone were treated for 1 hour with purified MT910 (IgG, kappa) anti-**CD2** **antibody** (Rieber et al., Leukocyte Typing II, Vol. I, pp. 233-242 (1986)) at a concentration of 1 ug/ml, or with purified MB40.5 (IgG1, kappa; Kawata et al., J. Exp. Med. 160:633-651 (1984)) **antibody** at the same concentration. MB40.5 recognizes a monomorphic HLA--ABC determinant and cross-reacts with African Green Monkey histocompatibility antigens; it was chosen because it represents an isotype-matched **antibody** recognizing a surface antigen of approximately the same abundance as the **CD2** antigen expressed by transfected cells. Sheep erythrocyte rosettes were observed in the presence of MB40.5, but not of MT910. Rosette inhibition was also observed with OKT11 **antibody**, and not with various other control **antibodies**.

DETDESC:

DETD(111)

In . . . and human thymocytes (Baxley et al., Clin. Exp. Immunol. 15:385-393 (1973)) have also been reported. COS cells transfected with the **CD2** expression clone were treated with either MT910 or with the control **antibody**, MB40.5, and exposed to erythrocytes from the species above. Rosettes were observed with horse, pig, dog, goat, sheep, rabbit, and. . .

DETDESC:

DETD(113)

Because it has been suggested on the basis of **antibody** blocking studies that LFA3 is the target structure for the **CD2** antigen (Shaw et al., Nature 323:262-264 (1986)), the ability of anti-LFA3 **antibody**

to prevent rosette formation was investigated. Transfected cells were exposed to human erythrocytes pretreated for 2 hours with either anti-LFA3 (IgG1, kappa) as ascites at 1:1000 dilution, or with a 10 ug/ml concentration of each of four isotype-matched nonagglutinating **antibodies** directed against human erythrocyte antigens as prevalent or more prevalent than LFA3:G10/B11 and D10, anti-K14 antigen, D6, anti-Wr.sup.b antigen; and F7/B9, anti-k antigen. Nichols et al., Vox Sang, in press. The erythrocytes were washed free of excess LFA3 **antibody**, but were allowed to form rosettes in the presence of the control **antibodies** to guard against possible loss of **antibody** blocking power by desorption. Rosette formation was observed in the presence of all four control **antibodies**, but not with erythrocytes pretreated with anti-LFA3.

DETDESC:

DETD(115)

A number of clones were isolated by the same expression technique used to clone **CD2** and characterized to varying degrees by **antibody** reactivity, nucleic acid restriction and sequence analysis, and immunoprecipitation. Representative clones were transfected into COS cells and analyzed for ability. . .

DETDESC:

DETD(123)

The previous example shows that cDNAs encoding surface antigens, such as the **CD2** antigen, can be isolated by the transient expression system of the present invention, in which COS cells transfected with cDNA libraries are allowed to attach to ("panned" on) **antibody**-coated plates. Plasmid DNA is recovered from cells adhering to the plates, transformed into E. coli, and the process is repeated, usually twice, to isolate the desired clone. Although powerful, this approach cannot be used when the monoclonal **antibodies** used for panning recognize determinants on the untransfected cells. This appears to be the case for anti-LFA3 monoclonal TS2/9. However,. . . polyoma virus replication-competent cells should allow almost all monoclonals to be used, since the probability of cross reaction between murine **antibodies** and murine cell surface determinants should usually be small.

DETDESC:

DETD(257)

B cell adhesion studies involving anti-epitope monoclonal **antibodies** have indicated that different epitopes of CD22 may participate in erythrocyte and monocyte adhesion and that different ligands may be. . . recognized on each cell type. B cell adhesion studies also suggest that CD22, in a manner analogous to T cell **CD2**, CD4 and CD8 adhesion to target cells, may promote recognition by the B cell antigen receptor by intensifying B cell-presenting. . .

US PAT NO: 5,502,167 [IMAGE AVAILABLE] L5: 11 of 23
TITLE: CDR grafted **humanised** **chimeric** T-cell antibodies

ABSTRACT:

A **humanised** **antibody** is provided in which the amino acid sequence of the CDRs is derived from the sequence of CDRs of a monoclonal **antibody** having the specificity of binding to resting and activated T-cells, inhibiting T-cell proliferation and lysing T-cells from mice transgenic for human **CD2** and in which sufficient of the amino acid sequence of each CDR has been retained to provide the same specificity for the **humanised** **antibody**.

SUMMARY:

BSUM(1)

The present invention relates to a **humanized** **antibody** which binds to resting and activated T cells, inhibits T cell proliferation and lyses T cells from mice transgenic for human **CD2**, to the preparation of such an **antibody** and to a pharmaceutical composition which contains the **antibody**.

SUMMARY:

BSUM(4)

The . . . the variable domains, and the constant domains, of the altered antibody may be derived from a human antibody. Such a **humanised** antibody elicits a negligible immune response when administered to a human compared to the immune response mounted by a human against a rat or mouse antibody. **Humanised** CAMPATH-1 antibody (Campath is a Trademark of The Wellcome Foundation Ltd.) is disclosed in EP-A-0328404.

SUMMARY:

BSUM(7)

According to one aspect the present invention provides a **humanised** **antibody** in which the amino acid sequence of the CDRs is derived from the sequence of the CDRs of a monoclonal **antibody** having the specificity of binding to resting and activated T-cells, inhibiting T-cell proliferation and lysing T-cells from mice transgenic for human **CD2** and in which sufficient of the amino acid sequence of each CDR has been retained to provide the same specificity for the **humanised** **antibody**.

SUMMARY:

BSUM(8)

According to another aspect of the present invention, there is provided a **humanised** antibody in which sufficient of the amino acid sequence of each CDR shown below is provided such that the antibody. . .

SUMMARY:

BSUM(19)

The . . . Nos: 3 to 8 and Seq ID Nos: 11 to 16 respectively are the

CDRs of the anti-human T cell **antibody** YTH 655(5)6. YTH 655(5)6 is a rat IgG2b monoclonal **antibody** which binds to resting and activated T cells, inhibits T cell proliferation and lyses T cells from mice transgenic for human **CD2**. The specificity of a **humanized** YTH 655 **antibody** can be determined by its ability to bind to resting and activated T cells, inhibit T cell proliferation and lyse T cells from mice transgenic for human **CD2**.

SUMMARY:

BSUM(20)

Suitably, the CDRs of a **humanised** antibody are the light chain CDRs 1 to 3 and the heavy chain CDRs 1 to 3 above. The amino. . .

SUMMARY:

BSUM(24)

A **humanised** antibody is prepared according to the invention by a process which comprises maintaining a host transformed with a first expression vector which encodes the light chain of the **humanised** antibody and with a second expression vector which encodes the heavy chain of the **humanised** antibody under such conditions that each chain is expressed and isolating the **humanised** antibody formed by assembly of the thus-expressed chains.

SUMMARY:

BSUM(26)
a DNA sequence encoding the light chain or the heavy chain of the **humanised** antibody;

SUMMARY:

BSUM(29)

Each . . . the antibody chain is expressed. Complementary antibody chains which are co-expressed in this way may then assembly to form the **humanised** antibody.

SUMMARY:

BSUM(30)

There are four general steps to **humanise** a monoclonal antibody. These are:

SUMMARY:

BSUM(32)
(2) designing the **humanised** antibody, i.e. deciding which antibody framework region to use during the **humanising** process;

SUMMARY:

BSUM(33)
(3) the actual **humanising** methodologies/techniques; and

SUMMARY:

BSUM(34)
(4) the transfection and expression of the **humanised** antibody.

SUMMARY:

BSUM(37)

To **humanise** an antibody only the amino acid sequence of antibody's heavy and light chain variable domains needs to be known. The. . .

SUMMARY:

BSUM(40)
Designing the **humanised** antibody

SUMMARY:

BSUM(41)

There are several factors to consider in deciding which human antibody sequence to use during the **humanisation**. The **humanisation** of light and heavy chains are considered independently of one another, but the reasoning is basically similar for each.

SUMMARY:

BSUM(45)
2. . . . also in the surrounding framework regions. The human variable domain which is most homologous is chosen as the framework for **humanisation**.

SUMMARY:

BSUM(47)
The actual **humanising** methodologies/techniques

SUMMARY:

BSUM(48)

An antibody may be **humanised** by grafting the desired CDRs onto a human framework according to EP-A-0239400. A DNA sequence encoding the desired reshaped antibody. . .

SUMMARY:

BSUM(50)

Alternatively, **humanisation** may be achieved using the recombinant polymerase chain reaction (PCR) methodology of WO 92/07075. Using this methodology, a CDR may. . .

SUMMARY:

BSUM(51)

In . . . to be performed. Thus, the amplified regions AB and CD may undergo gene splicing by overlap extension to produce the **humanised** product in a single reaction.

SUMMARY:

BSUM(55)
(a) . . . heavy or light chain, the variable domain comprising framework regions from a human antibody and the CDRs required for the **humanised** antibody of the invention;

SUMMARY:

BSUM(59)

Preferably . . . in step (a) encodes both the variable domain and the or each constant domain of the human antibody chain. The **humanised** antibody can be recovered and purified. The cell line which is transformed to produce the altered antibody may be a. . .

SUMMARY:

BSUM(60)

Although the cell line used to produce the **humanised** antibody is preferably a mammalian cell line, any other suitable cell line, such as a bacterial cell line or a. . .

SUMMARY:

BSUM(61)

Once . . . 98 to 99% or more homogeneity most preferred, for pharmaceutical uses. Once purified, partially or to homogeneity as desired, a **humanised** antibody may then be used therapeutically or in developing and performing assay procedures, immunofluorescent stainings, and the like (see, generally,. . .

SUMMARY:

BSUM(62)

The . . . state. Generally, where the cell linked to a disease has been identified as bearing the T cell antigen, then the **humanised** antibodies capable of binding the T cell antigen are suitable. For example, typical disease states suitable for treatment include graft. . .

SUMMARY:

BSUM(66)

A . . . chain, etc., or an agent active at the cell surface, such as the phospholipase enzymes (e.g., phospholipase C). See, generally, "**Chimeric** Toxins," Olsnes and Phil, Pharmac. Ther., 25:335-381 (1982), and "Monoclonal Antibodies for Cancer Detection and Therapy," eds. Baldwin and Byers,. . .

SUMMARY:

BSUM(67)

The delivery component of the immunotoxin is a **humanised** antibody according to the present invention. Intact immunoglobulins or their binding fragments, such as Fab, are preferably used. Typically, the. . .

SUMMARY:

BSUM(68)

The invention further provides a pharmaceutical composition comprising a pharmaceutially acceptable carrier or diluent and, as active ingredient, a **humanised** antibody according to the invention. The composition may be comprise an immunotoxin according to the invention. The **humanised** antibody, immunotoxin and pharmaceutical compositions thereof of this invention are particularly useful for parenteral administration, i.e., subcutaneously, intramuscularly or intravenously.

SUMMARY:

BSUM(76)

For . . . or unlabelled. Unlabelled antibodies can be used in combination with other labelled antibodies (second antibodies) that are reactive with the **humanised** antibody, such as antibodies specific for human immunoglobulin constant regions. Alternatively, the antibodies can be directly labelled. A wide variety. . .

SUMMARY:

BSUM(77)

Kits . . . in the protection against or detection of a cellular activity or for the presence of a selected antigen. Thus, a **humanised** antibody of the present invention may be provided, usually in a lyophilized form in a container, either alone or in. . . in from about 1 to 99% wt. of the total composition. Where a second antibody capable of binding to the **chimeric** antibody is employed in an assay, this will usually be present in a separate vial. The second antibody is typically. . .

DRAWING DESC:

DRWD(2)

Binding of **Humanized** YTH 655 to MF14 cells.

DRAWING DESC:

DRWD(3)

The activity of **humanized** YTH 655 (HUMCD2) was assayed by FACS using an activated T cell line called MF14. A **chimeric** YTH 655 (CHIMCD2) containing a human IgG1 constant region and YTH 655 variable regions was

used as a control. Cells were first incubated with either **chimeric** YTH 655 or **humanized** YTH 655. After washing, the cells were incubated with a commercially available anti-human FITC then analyzed by FACS. The figure shows that the binding of **humanized** YTH 655 is equivalent to binding of **chimeric** YTH 655 and that the **humanized** YTH 655 binding can be titrated. The antigen specificity of the **humanized** monoclonal antibody, therefore, has been retained.

DETDESC:

DETD(12)

Using . . . HSIGKVII light chain (EMBL data base; Klobeck, H. G. EMBL data library submitted 7th Apr., 1986) were chosen for the **humanisation** process.

DETDESC:

DETD(13)
Construction of the **humanised** heavy and light chain genes

DETDESC:

DETD(14)

The **humanised** heavy and light chains were constructed following the method of Lewis and Crowe (Gene 101, 297-302, 1991).

DETDESC:

DETD(26)

The initial template for the PCR was previously **humanized** Hum DXC2 light chain, a human kappa light chain with HSIGKVII frameworks which had subsequently undergone site-directed mutagenesis to replace. . .

DETDESC:

DETD(27)

Four . . . as above, and a quarter of each combined in a recombinant PCR reaction using primers A.sub.L and H.sub.L. The final **humanised** light chain recombinant PCR product, AH.sub.L, was cloned into the HindIII site of pUC-18 (BR.sub.L) following the method of Crowe. . .

DETDESC:

DETD(38)

The initial template for the PCR was **humanised** anti-CD4 heavy chain (on KOL framework; WO 92/05274; Gorman et al., Proc. Natl. Acad. Sci. USA 88, 1991) subsequently converted. . . to H.sub.H. Oligonucleotides A.sub.H and H.sub.H were designed with HindIII and EcoRI sites respectively to enable initial cloning of the **humanised** variable region, and a SpeI site was introduced into the KOL framework 4 (FR4) region of oligonucleotide G.sub.H to facilitate. . . choice. The SpeI site altered the threonine residue at position 109 (numbering according to Kabat et al., 1987) of the **humanised** anti-CD4 heavy chain template

(proline in KOL) to a leucine residue (four out of the six human heavy J-minigenes possess a leucine at this position; Kabat et al., 1987). The **humanised** heavy chain variable region recombinant PCR product was cloned into HindIII/EcoRI-cut pUC-18 (BR.sub.L), and plasmid isolates of the correct sequence were chosen. The FR4 and c1 constant regions of the **humanised** anti-CD4 heavy chain were PCR cloned into pUC-18 (BR.sub.L) using oligonucleotide primers X.sub.H (SEQ ID NO: 33) and Y.sub.H (SEQ. . . into pUC-18, and plasmid isolates of the correct sequence were selected. The complete heavy chain was subsequently reconstituted from the **humanised** variable region and .gamma.1 constant region clones using the engineered FR4 Spe1 site.

DETDESC:

DETD(39)

Humanized YTH 655 heavy and light chains were cloned into a eukaryotic expression vector under human cytomegalovirus promoters and expressed transiently in COS cells at 200 ng/ml as determined by IgG ELISA. A stable cell line expressing **humanized** YTH 655 heavy and light chains was made by transfecting NSO cells with the same eukaryotic expression vector used for the COS cell transfections. Binding to YTH 655 and a **chimeric** YTH 655 containing human IgG1 constant region and YTH 655 variable region were shown by FACS analysis to bind an activated T cell line called MF14. **Humanized** YTH 655 [4 ug/mg] binding to MF14 cells was equivalent to binding of the rat YTH 655 [4 ug/ml] and **chimeric** YTH 655 [4 ug/ml] as determined by FACS (Weir D.M. 1985 Handbook of Experimental Immunology Vol 1 and 2 4th Ed-Blackwell Scientific Publication, Oxford). The antigen specificity of the **humanized** monoclonal antibody, therefore, has been retained. Binding of **humanized** YTH 655 to MF14 cells was shown to be concentration dependent by FACS analysis.

CLAIMS:

CLMS(1)

We claim:

1. A **humanised** **antibody** that specifically binds resting and activated T-cells, inhibits T-Cell proliferation and lyses T-cells from mice transgenic for human **CD2**, the heavy and light chain variable domains of said **antibody** are composed of framework and complementary determining regions, wherein light chain complementary determining region 1 has the amino acid sequence. . .

CLAIMS:

CLMS(4)

4. A DNA sequence encoding the light chain or the heavy chain of the **humanised** antibody of claim 1.

US PAT NO: 5,439,665 [IMAGE AVAILABLE] L5: 12 of 23

SUMMARY:

BSUM(24)

Use . . . used interchangeably therefor in this discussion. Antibodies can be whole immunoglobulin of any class, e.g., IgG, IgM, IgA, IgD, IgE, **chimeric** antibodies or hybrid antibodies with dual or multiple antigen or epitope specificities, or fragments, e.g., F(ab').sub.2, F(ab).sub.2, Fab', Fab and. . .

SUMMARY:

BSUM(32)

Suitable anti-T-cell **antibodies** include **antibodies** which bind to the CD1, **CD2**, CD4, CD6, CD7 or CD8 antigens. Preferred anti-T-cell **antibodies** are those that bind to the CD3 antigen and the CD5 antigen. A preferred **antibody** that binds to both monocyte and granulocyte antigens is a monoclonal which binds in particular to the CDW14 antigen. Preferred **antibodies** that bind to B-cells include **antibodies** that bind to the CD19 or CD21 antigens. **Antibodies** that bind to activated T-cells include monoclonals that bind to the CD25 or CD26 antigens. The CD antigens are leukocyte determinants that define **antibodies** having particular leukocyte specificities. A pair of **antibodies** that bind to the same epitope on the same CD antigen will cross-block binding to the same leukocyte cell types. **Antibodies** that bind specifically to the Ia (HLA-DR) histocompatibility antigen common to monocytes, B-lymphocytes and activated T-lymphocytes are classified as anti-HLA-DR Class II **antibodies**, and are of particular utility for certain applications.

US PAT NO: 5,426,029 [IMAGE AVAILABLE] L5: 13 of 23

SUMMARY:

BSUM(7)

TABLE I

LEUKOCYTE SURFACE MOLECULES

Leukocyte Surface Marker	Expression	Detection Monoclonal **Antibodies**	References
T cell Antigen Receptor			
	All T cells and T cell subsets	T40/25, .alpha.F1, .beta.F1,	1, 2,. . . Langerhans
		OKT6	
	Cells, Leukemia Cells	NAI/34	
NK cell receptor			
	NK cells	NC-37 specific **antibodies**	7
Cell Adhesion Molecules			
CD2	All T cells	OKT11	8, 9, 10
		Leu5	
		B67.1	

CD58 (LFA-3) Leukocytes, epithelial
TS2/9 11
CD3 Pan. . .

SUMMARY:

BSUM(99)

Several other cell surface markers which are primarily present on T cells have also been found in soluble form. **CD2**, a T cell surface molecule present in all normal T cells and a receptor for sheep red blood cells, has. . . et al., 1983, J. Exp. Med. 159:752-766). Leu-1, another T cell surface molecule, was measured in serum following anti-Leu-1 monoclonal **antibody** treatment (Miller, R. A., et al., 1982, New Engl. J. of Med. 306:517-520). Oh et al. (1985, supra) reported that less than half of the patients with malignancies in their study presented elevated levels of soluble **CD2** receptor in their serum.

DETDESC:

DETD(48)

In one embodiment, the monoclonal antibodies may be human monoclonal antibodies, **chimeric** human-mouse (or other species) antibodies, or **humanized** monoclonal antibodies. Human monoclonal antibodies may be made by any of numerous techniques known in the art (e.g. Teng et. . . Proc. Natl. Acad. Sci. U.S.A. 80:7308-7312; Kozbor et al., 1983, Immunology Today 4:72-79; Olsson et al., 1982, Meth Enzymol. 92:3-16). **Chimeric** antibody molecules may be prepared containing a mouse (or human, or rat, or other species) antigen-binding domain with human constant regions (Morrison et al., 1984, Proc. Natl. Acad. Sci. U.S.A. 81:6851; Takeda et al., 1985, Nature 314:452). **Humanized** antibodies may be recombinantly prepared such that only the hypervariable domains are non-human sequences.

DETDESC:

DETD(300)

The supernatants of various cultured cells were assayed for soluble **CD2** using two monoclonal **antibodies** which define different epitopes of the **CD2** (T11) molecule. Samples were assayed using a sandwich immunoassay format as previously described, in which monoclonal **antibodies** B67.6.1.1. and B67.1.1.1. (Perussia, B., et al., 1983, J. Immunol. 130:2142) were used as the capture and detection **antibodies**, respectively, and vice versa.

US PAT NO: 5,411,861 [IMAGE AVAILABLE] L5: 14 of 23

ABSTRACT:
A . . . analysis method for mapping protein epitopes is disclosed. This method has been used to identify the binding sites for 16 anti-**CD2** and anti-CD4 monoclonal **antibodies**. The powerful, rapid, and simple method of the present invention allows isolation of a very large number of mutants, and is applicable to any intracellular or surface protein for which a cDNA and monoclonal **antibodies** are available. The present method is especially useful in ligand binding site studies for the design of new ligands and. . .

SUMMARY:

BSUM(4)

Resting human T cells bind sheep erythrocytes via a T cell specific 50 kD cell surface protein called **CD2** (Bach, J. F., et al., Transplantation 8:265-280 (1969); Howard, F. D., et al., J. Immunol. 126:2117-2122 (1981)). This phenomenon has. . . physiological targets (Shaw, S., et al., Nature 323:262-264 (1986)), have led to the identification of a specific molecular ligand for **CD2** which is a widely distributed surface protein called, in the human case, LFA-3. **CD2**/LFA-3 interactions mediate cytolytic target conjugation (Shaw, S., et al., Nature 323:262-264 (1986)), thymocyte-epithelial adhesion (Vollger, et al., (1987)), and the mixed lymphocyte reaction (Martin, P. J., et al., J. Immunol. 131:180-185 (1983)). In addition, a broader role for the **CD2** antigen has been suggested by the discovery that certain combinations of anti-**CD2**-monoclonal **antibodies** can directly activate mature T cells via an antigen-independent pathway.

SUMMARY:

BSUM(5)

An understanding of the molecular interaction between **CD2** and LFA-2 or anti-**CD2** **antibodies** would be useful in correlating physiological function with structure. This type of information is useful in designing compounds that can. . . in multiple binding assays (Geysen, H. M., et al., Science 235:1184-1190 1987)). In order to identify specific residues important for **antibody** binding, variants of the peptide are synthesized with substitutions at each position. The synthetic peptide strategy has several limitations. If the **antibody** derives its affinity from interaction with disparate portions of the polypeptide backbone or with a novel conformation of the backbone, the peptide will be unable to mimic the entire protein in binding to the **antibody**. In order to identify individual residues contacted by the **antibody**, an extremely large number of peptide variants must be synthesized. The most exhaustive study to date involved the assay of. . .

SUMMARY:

BSUM(14)

The method of the present invention has been used to define the regions through which the **CD2** antigen binds to anti-**CD2** monoclonal **antibodies** and to define the binding sites on the CD4 antigen for the human immunodeficiency virus (HIV).

SUMMARY:

BSUM(15)

CD2 cDNA mutations were selected which lead to loss of **CD2**-**antibody** reactivity. The pattern of amino acid substitutions in the mutants defines three distinct regions of the **CD2** molecule: one epitopic region recognized by group I and II **antibodies**; a second

epitopic region recognized by group III **antibodies**; and a third epitopic region recognized by group IV **antibodies**. Comparison of amino acid residues important for **antibody** binding and amino acid residues important for LFA-3 binding indicates that group I and II **antibodies** intersect with one portion of the LFA-3 binding site; that group III **antibodies** interact with another portion of the LFA-3 binding site; and that group IV **antibodies** interact with still another portion, which is not involved in LFA-3 binding. In addition, the close correspondence between the effects of individual substitutions on group I **antibody** and LFA-3 binding suggests that group I **antibodies** mediate their effect on T cell activation by mimicking the effects of LFA-3 binding.

DRAWING DESC:

DRWD(6)

FIG. 2A presents the predicted sequence of the mature **CD2** protein. The transmembrane region is underlined with a dark bar. The **antibodies** used are shown along the left margin. The symbols under the primary sequence indicate the sensitivity of each **antibody** to changes at that position, A "0+ indicates that a mutant was obtained with a substitution at that position or that indirect immunofluorescence of mutants obtained with another **antibody** showed a sensitivity to substitution at that position. A "+" indicates that a substitution at that position was tested and was not found to affect **antibody** reactivity. The "=" symbol means that only proline at that position affected reactivity. FIG. 2B is a hydrophobicity plot for the **CD2** protein. Above the central horizontal line are hydrophobic regions; below are hydrophilic regions of the protein. The three epitopic regions. . .

DRAWING DESC:

DRWD(7)

FIG. 3A-1, 3A-2 and 3B present the mutant collection defining epitope regions of **CD2**. The sequence of short stretches of the **CD2** polypeptide which include each of the two major epitopic regions are shown. The amino acid substitution variants acquired by mutant. . . selection are shown underneath each wild-type sequence. FIG. 3A-1 and 3A-2 presents the sequence of epitope region 1 of the **CD2** polypeptide. FIG. 3B presents the sequence of epitope region 2 of the **CD2** polypeptide. The columns on the right indicate (from left to right) the **antibody** used for negative selection and the **antibody**(ies) used for positive selection. "All 16" means that all 16 of the monoclonals in FIG. 2A were combined for the positive selection step. "7 others"[means that seven **antibodies** other than 35.1 recognizing the first epitopic region were combined for the positive selection step. The variants directly under the **CD2** sequence were obtained by selecting mutants from a pool of plasmids mutagenized throughout the portion of the cDNA encoding the. . .

DRAWING DESC:

DRWD(9)

FIG. . . . are from the pBR322 origin of replication, 588-1182 from the M13 origin, 1183-1384 from the SupF gene, 1385-2238 from the

chimeric cytomegalovirus/human immunodeficiency virus promoter, 2239-2647 from the replaceable fragment or stuffer, 2648-3547 from plasmid pSV2 (splice and polyadenylation signals), and. . .

DETDESC:

DETD(28)
Determination of **CD2** LFA-3 and **Antibody** Binding Domains

DETDESC:

DETD(29)

Binding . . . COS cells were transfected with a pool of mutagenized plasmids, cultured for 48 hours, harvested and treated sequentially with an anti-**CD2** monoclonal **antibody** (i.e., with a monoclonal **antibody** recognizing the epitope whose loss is desired), rabbit anti-mouse immunoglobulin **antibody** and complement. This step is referred to as the negative selection step and is represented as step (i) in FIG.. . .

DETDESC:

DETD(30)

Because . . . 80:3010-3014 (1983), a positive selection step was carried out as follows: the cells spared by complement treatment were treated with **antibody**(ies) recognizing a distinct **CD2** epitope(s) and allowed to adhere to dishes coated with goat anti-mouse immunoglobulin **antibody**. Wysocki, L. J. and Sato, V. L., Proc. Natl. Acad. Sci. USA, 75:2844-2848 (1978). **Antibodies** used for isolation of epitope-loss mutants are shown in Table 1.

DETDESC:

DETD(40)

The pattern of amino acid substitutions in the mutants defines three distinct regions of the **CD2** molecule comprising many sequence variants: **antibodies** that participate in activation and block erythrocyte adhesion bind to a first region; **antibodies** that only block adhesion bind to a second region; and **antibodies** that participate in activation but do not block adhesion bind to a third region.

DETDESC:

DETD(42)

FIG. 3A in particular shows the mutant collection defining epitope region 1. **CD2** residues 42-56 are shown above the amino-acid substitution encoded by each mutant. The first column on the right shows the **antibody** used for negative selection. The second column shows the positive selection **antibody**(ies). "All 16" indicates that all 16 monoclonals in Table 1 were combined and used for the positive selection step. "7 others" means that the seven **antibodies** other than 35.1 recognizing the first epitopic region were combined for the positive selection step. Variants directly under the **CD2** sequence were

obtained by selecting mutants from a pool of plasmids mutagenized throughout the extracellular domain of the protein. The. . . random mutagenesis covering the span of the bars. The mutant collection defining epitope region 2 is shown in FIG. 3B. **CD2** residues 86 through 100 are shown above the mutant substitutions. Other notations are as in FIG. 3A.

DETDESC:

DETD(44)

The ability of the mutant **CD2** proteins to promote LFA-3 mediated adhesion of human erythrocytes to transfected COS cells was measured by a qualitative erythrocyte rosette. . . non-rosetting. Many of the mutations leading to changes in region 1 and 2 (reactive with groups I, II and III **antibodies**) dramatically reduced rosetting. To examine this further, a few mutants were created by specific site-directed oligonucleotide missense mutagenesis. Substitution of. . . positions 46, 47, and 48 of epitope region 1 demonstrated a striking correlation between the binding of the group I **antibody** Mab 9.6 and erythrocyte adhesion. Lys46Asn/Ala showed a modest effect on both Mab 9.6 and erythrocyte binding; Lys47Asn/Ala had no. . .

DETDESC:

DETD(45)

Subsequent experiments with other **antibodies** and other mutants showed that Lys48 plays a major role in the interaction of **CD2** with group I **antibodies** and LFA-3 (FIGS. 2A-2B and 4). For example, the mutant Lys48Gly is unreactive with all of the group I **antibodies**, and none of the **CD2** molecules substituted at Lys48 has any detectable rosetting activity. The behavior of substitutions at Lys48 constitutes one of the strongest pieces of evidence that group I **antibodies** mimic the effect of LFA-3 binding in provoking T cell proliferation.

DETDESC:

DETD(50)

For . . . changes at Ile49. Similarly, both Mab 9.6 and LFA-3 cannot bind to the Gln51Leu variant, which nonetheless is recognized by **antibodies** 7E10 and 9-2. **CD2** having a Gln51Arg substitution is unreactive with 7E10 and 9-2 but binds LFA-3 indistinguishably from wild-type. In the second epitope region, the Tyr91Asp mutation causes loss of rosetting, but **antibody** NU-TER binding is not affected, even though many substitutions at position 92 eliminate NU-TER reactivity.

DETDESC:

DETD(52)

To isolate a 35.1 mutant other than Gln51Pro, only the **antibodies** which fail to bind to this variant were used for positive selection. After three cycles of enrichment, a single 35.1. . . was altered in all three bases of the original codon. The unusual nature of this mutation suggests that the 35.1 **antibody** derives its affinity from multiple features of the **CD2** conformation, so that substitution for a single feature only rarely leads to greatly lowered affinity. The

Gln51Pro mutation may eliminate several of these interactions by gross alteration of the local secondary structure. Because the affinity of the 35.1 **antibody** is comparable to that of **antibody** 9.6 (Martin, P. J. et al., J. Immunol. 13:180-185 (1983)), it appears that the unusual mutational spectrum of this **antibody** arises from a qualitatively different mode of binding and not simply a stronger interaction. Another group II **antibody**, T11/3PT2H9, also gave Gln51Pro mutations exclusively when all 16 monoclonals were pooled for the positive selection step.

DETDESC:

DETD(53)
CD2 Group IV **Antibody** Epitope

DETDESC:

DETD(54)

Only one mutant was obtained for the group IV **antibodies**, a Tyr140Asn/Gln141His double substitution. However, group IV **antibodies** react only weakly with the **CD2** molecule expressed on COS cells, a situation reminiscent of the weak reactivity of group IV **antibodies** with **CD2** on unactivated T cells, (Meuer, S. C., et al., Cell (1984) 36:897-906). Prior activation of T cells or incubation with a group I **antibody** is necessary to make the group IV **antibody** epitope available (Meuer, S. C. et al., supra). The rapid acquisition of group IV **antibody** reactivity suggests that it is caused by a conformational change in the molecule and not by de novo synthesis of. . .

DETDESC:

DETD(55)

Each of the monoclonal **antibodies** in this study gave a contiguous linear pattern of mutational variation. All three epitopic regions are hydrophilic as would be expected for an exposed portion of the molecule available for **antibody** binding (FIG. 2B). Several alternatives may be put forth to explain why only a few restricted portions of the molecule give rise to multiple independent **antibodies**. For example, a portion of the first epitope is predicted to form an alpha helix with hydrophilic residues on one. . . (1985) Proc. Natl. Acad. Sci. USA 82:7048), and recognition of this region by mouse helper T cells may focus the **antibody** response. In the region corresponding to epitope region 2 (FIG. 3b), three potential N-linked glycosylation sites are found in the rat **CD2** sequence (Williams, A. F. et al. (1987) J. Exp. Med. 165:368-380) which are not present in the human sequence.. . . reducing the number of mouse suppressor T cells which might cross-react with the human sequence. Alternatively, the restricted spectrum of **antibody** binding sites may arise from the prior selection of **antibodies** for erythrocyte receptor reactivity.

DETDESC:

DETD(73)

Spheroplasts . . . abandoned, and Ser. No. 553,759, filed Jul. 13, 1990, both now abandoned. Forty-eight hours following fusion, the COS

cells expressing **CD2** were detached from the dish in PBS/1 mM EDTA. The COS cells from six 60-mm dishes were then incubated in PBS, 10% calf serum, 0.02% sodium azide (PBS-FBS) containing a 1/1000 dilution of ascites fluid of the negative selection **antibody**. All **antibody** incubations were performed in 1 ml of PBS-FBS for 30 minutes on ice and were followed by centrifugation through a cushion of 2% Ficoll in PBS. The cells were then incubated with 5 .mu.g/ml rabbit antimouse Ig **antibody** (Rockland). Two mls of 50% rabbit complement (Pel-Freeze) in DME (GIBCO) were then added and incubated at 37.degree. C. for. . . cells through a 5 ml ficoll cushion. The cells were then incubated with a 1/1000 dilution of the positive selection **antibody** and added to sheep antimouse immunoglobulin (Cooper Biomedical) coated dishes (Wysocki, L. G. and Sato, V. L. (1978) Proc. Natl.. . . application Ser. No. 160,416, now abandoned. The mutant phenotypes were assayed by sequential indirect immunofluorescence using first the negative selection **antibody** followed by the positive selection **antibody**.

US PAT NO: 5,364,612 [IMAGE AVAILABLE] L5: 15 of 23

SUMMARY:

BSUM(36)

The . . . single mammalian species or of a genetically-engineered combination of species (such as a combination of human and rodent, in so-called **humanized** or chimerized antibodies). Antibodies can be whole immunoglobulin of any class, e.g., IgG, IgM, IgA, IgD, IgE, **chimeric** or hybrid antibodies with dual or multiple antigen or epitope specificities, or fragments, e.g., F(ab').sub.2, F(ab).sub.2, Fab, Fab', Fv, and. . .

SUMMARY:

BSUM(43)

Suitable anti-T-cell **antibodies** include **antibodies** which bind to the CD1, **CD2**, CD4, CD6, CD7 or CD8 antigens. Preferred anti-T-cell **antibodies** are those that bind to the CD3 antigen and the CD5 antigen. A preferred **antibody** that binds to both monocyte and granulocyte antigens is a monoclonal which binds in particular to the CDW14 antigen. Preferred **antibodies** that bind to B-cells include **antibodies** that bind to the CD19 or CD21 antigens. **Antibodies** that bind to activated T-cells include monoclonals that bind to the CD25 or CD26 antigens. The CD antigens are leukocyte determinants that define **antibodies** having particular leukocyte specificities. A pair of **antibodies** that bind to the same epitope on the same CD antigen will cross-block binding to the same type of leukocyte. **Antibodies** that bind specifically to the Ia (HLA-DR) histocompatibility antigen common to monocytes, B-lymphocytes and activated T-lymphocytes are classified as anti-HLA-DR Class II **antibodies**, and are of particular utility for certain applications.

US PAT NO: 5,296,353 [IMAGE AVAILABLE] L5: 16 of 23

SUMMARY:

BSUM(14)

The . . . couple stimulation of the receptor with the signal transduction pathways. B. A. Irving et. al., Cell. 64, 891 (1991). A **chimeric** protein linking the extracellular and transmembrane domains of CD8 to the cytoplasmic domain of the .zeta. chain was constructed. The **chimeric** protein activated the appropriate signal transduction pathways in the absence of CD3 .gamma., .delta., and .epsilon.. Therefore the role of. . .

DETDESC:

DETD(10)

The **antibody** to a T lymphocyte surface receptor can be made by well known and conventional methods, for example those described in. . . A. M. Jruisbeek, D. H. Margulies, E. M. Shevach and W. Strober (eds.), Green Publishing Associates and Wiley-Interscience, 2.4.1-2.10.3 (1991). **Antibodies** to a surface receptor that can be used alone, or in combination with other **antibodies** to different T cell surface receptors, in a method for the activation of T lymphocytes, include, but are not limited to, anti-**CD2**, anti-CD3, anti-CD4, anti-CD5, anti-CD6, anti-CD7, anti-CD8, anti-CD28, anti-CDw29, or anti-CD45R. It is preferably an anti-CD3 MAb. The anti-CD3 MAb can. . . about 10 ng/ml, or less, anti-CD3 MAb. Mouse anti-human OKT3 is available from the Ortho Division of Johnson and Johnson. **Humanized** versions of the **antibodies** will have utility for T cell activation in vivo during treatment.

US PAT NO: 5,292,636 [IMAGE AVAILABLE] L5: 17 of 23

SUMMARY:

BSUM(165)

. . .

TABLE I

T CELL SURFACE MARKERS T Cell Surface Marker	Molecular Weight (kd)	Detection Expression	Monoclonal **Antibody** Reference
T Cell Antigen Receptor. . .	90	All T Cells	T40/25 Brenner, M. B., et al., 1984, J.
	94	Transferrin Receptor (Activated T Cells)	OKT9 Reinherz, E. L., et al., 1980, PNAS USA 77:1588-1592
CD2	50	All T Cells	OKT11 Verbi, W., et al.,

Leu 5 1982, Eur. J.
Immunol. 12:81-86

VLA-1. . .

SUMMARY:

BSUM(178)

Several other cell surface markers which are primarily present on T cells have also been found in soluble form. **CD2**, a T cell surface molecule present in all normal T cells and a receptor for sheep red blood cells, has. . . et al., 1983, J. Exp. Med. 159:752-766). Leu-1, another T cell surface molecule, was measured in serum following anti-Leu-1 monoclonal **antibody** treatment (Miller, R. A., et al., 1982, New Engl. J. Med. 306:517-520). Oh et al. (1985, supra) reported that less. . .

DETDESC:

DETD(34)

In one embodiment, the monoclonal antibodies may be human monoclonal antibodies or **chimeric** human-mouse (or other species) monoclonal antibodies. Human monoclonal antibodies may be made by any of numerous techniques known in the. . . Proc. Natl. Acad. Sci. U.S.A. 80:7308-7312; Kozbor et al., 1983, Immunology Today 4:72-79; Olsson et al., 1982, Meth. Enzymol. 92:3-16). **Chimeric** antibody molecules may be prepared containing a mouse (or rat, or other species) antigen-binding domain with human constant regions (Morrison. . .

DETDESC:

DETD(510)

The supernatants of various cultured cells were assayed for soluble **CD2** using two monoclonal **antibodies** which define different epitopes of the **CD2** (T11) molecule. Samples were assayed using a sandwich immunoassay format as previously described, in which monoclonal **antibodies** B67.6.1.1. and B67.1.1.1. (Perussia, B., et al., 1983 J. Immunol. 130:2142) were used as the capture and detection **antibodies**, respectively, and vice versa.

US PAT NO: 5,225,540 [IMAGE AVAILABLE] L5: 18 of 23

DRAWING DESC:

DRWD(2)

FIG. . . . chromogenic substrate S-2251 following incubation of t-PA for 1 h at 37.degree. in the presence of: (.DELTA.)AE5, (O) BA10, (.quadrature.) **CD2**, ( ) DB10, ( ) EG2, ( ) MOPC-21 and ( ) no **antibody**. All t-PA concentrations are reported in international units (IU) by comparison with the International Reference Preparation for t-PA.

DETDESC:

DETD(3)

The . . . in ELISAs using t-PA-coated microtitre wells, and in a solid phase RIA where the binding of iodinated t-PA to the **antibodies** was displaced by excess unlabeled t-PA. This RIA was employed to determine binding constants for each t-PA specific **antibody**, which ranged from 4.9.times.10.sup.8 M.sup.-1 to 2.3.times.10.sup.9 M.sup.-1. This panel of **antibodies** was broadly classified into three categories based on their different effects on both the plasminogen activator activity and the amidolytic activity of t-PA, as detailed in Example 3. **Antibodies** AE5, BA10 and EG2, which displayed negligible or small inhibitory effects in these assays, comprise one broad class characterized by their recognition of epitopes remote from the catalytic site of t-PA. **CD2**, on the basis of its near total inhibition of t-PA activity in both assays, is apparently directed to an epitope. . .

DETDESC:

DETD(4)

T-PA . . . disulfide bond to the L-chain, at the C-terminal end (Pennica et al. (1983) Nature 301:214-221). Recent studies using site-specific monoclonal **antibodies** (Holvoet et al. (1986) Eur. J. Biochem. 158:173-177) and t-PA deletion mutant proteins (MacDonald et al. (1986) Gene 42:59-67) have. . . solely responsible for the substrate specificity and the serine protease activity of the molecule. Clearly then, the epitope recognized by **CD2**, and probably that recognized by DB10, reside in the L-chain. Studies have also revealed that a PAI binding site on. . . basis of this information, one would predict in advance the exact pattern of inhibition actually exhibited by this panel of **antibodies** on the t-PA-PAI interaction: **CD2**>DB10>EG2,AE5,BA10.

DETDESC:

DETD(5)

In its properties, therefore, **CD2** resembles monoclonal **antibodies** generated by Loskutoff and coworkers (Schleef et al. (1986) Thromb. Haemostasis 56:328-332) and Collen and coworkers (Holvoet et al. (1987). . . and the distinction between this free (active) and complexed t-PA (inactive) is important in determining fibrinolytic activity of such samples. **CD2**, because of its recognition of the PAI binding domain on t-PA, represents a reagent capable of distinguishing free t-PA from t-PA-inhibitor complexes, unlike **antibodies** AE5, BA10 and EG2.

DETDESC:

DETD(6)

Another application of these **antibodies** is for analyzing and altering the regulation of t-PA activity. The regulation of fibrinolysis in vivo is dependent on the. . . Biochem. 32:169-178). The nature of the interaction between t-PA and these four proteins has not been fully clarified as yet. **Antibodies** directed to each of these protein binding domains on the t-PA molecule would constitute extremely useful reagents for inhibiting these protein interactions so that their role in regulating t-PA activity can be assessed. The **CD2** epitope is localized to the catalytic site of t-PA.

DETDESC:

DETD(10)

The . . . Proc. Natl. Acad. Sci. USA 77:6841-6845; Satoh et al. (1983) N. Engl. J. Med. 309: 217-220); or 3) utilizing human-mouse **chimeric** antibodies produced by genetic engineering techniques (Oi et al. (1986) BioTechniques 4:214-221). Furthermore, the recommended administration of t-PA (or, in. . .

DETDESC:

DETD(21)

Supernatants . . . from four separate fusions of the P3 myeloma cells with spleen cells of t-PA-immunized Balb/c mice were screened for specific **antibody** production by ELISA using t-PA-coated plates. Hybridoma cells from 11 positive wells were cloned by limiting dilution, and five of these clones producing **antibody** to t-PA were chosen for further studies. These **antibodies**, designated AE5, BA10, **CD2**, DB10 and EG2, were classed as IgG1s in typing ELISAs.

DETDESC:

DETD(25)

For . . . 25 and 40% of 3 ng [.sup.125 I]t-PA in the solid phase RIA. Standard curves were then generated for each **antibody** using these amounts of **antibody** and [.sup.125 I]t-PA, and five increasing concentrations of unlabeled t-PA. Affinity constants as calculated according to the method of Muller (op. cit.) are: AE5, 4.9.times.10.sup.8 M.sup.-1 ; BA10, 7.8.times.10.sup.8 M.sup.-1 ; **CD2**, 2.3.times.10.sup.9 M.sup.-1 ; DB10, 8.4.times.10.sup.8 M.sup.-1 ; EG2, 1.3.times.10.sup.9 M.sup.-1. From standard curves, it is concluded that the sensitivity limits in immunoassays for t-PA with these **antibodies** ranges between approximately 1 to 10 ng of t-PA per 100 .mu.l assay, or 10 to 100 ng of t-PA per ml of sample. With the exception of DB10, the **antibodies** did not discriminate between one-chain and two-chain forms of t-PA. DB10 displayed approximately ten-fold lower affinity for the two-chain species. Urokinase solutions up to 10 .mu.l/ml did not interfere in the assay with any of the **antibodies**.

DETDESC:

DETD(30)

The plasminogen activator activity of t-PA, before and after preincubation with a ten-fold molar excess of monoclonal **antibodies**, was measured spectrophotometrically relying on the chromogenic substrate S-2251. In view of the comparable affinities of the **antibodies** for t-PA, this same twenty-fold excess was used for all the **antibodies**. On the basis of the data shown in FIG. 1, this panel of **antibodies** could be broadly subdivided into three classes: complete inhibitors (**CD2**), partial inhibitors (DB10), and those with limited effect on the activity (AE5, BA10 and EG2). As used herein, "limited effect" means less than 10% inhibition. An irrelevant IgG1 **antibody** (MOPC-21) had no effect on t-PA activity in this assay indicating the specificity of

the t-PA **antibody** effects.

DETDESC:

DETD(31)

Since . . . either of two sites on t-PA: the catalytic site or the fibrin binding domain. To investigate these possibilities for the **antibodies** **CD2** and DB10, and to examine further the epitopes recognized by this panel of monoclonal **antibodies**, the fibrin-independent amidolytic activity of t-PA following incubation with each of the **antibodies** was measured. This assay relies on the ability of t-PA to cleave the chromogenic substrate S-2288, and activity is not. . . the presence of fibrin. FIG. 2 shows a similar pattern was observed in this assay as in the S-2251 assay; **CD2** totally inhibited the amidolytic activity of t-PA; DB10 was partial inhibitory; while AE5, BA10 and the control **antibody** MOPC-21 had negligible effects. EG2 slightly enhanced the amidolytic activity of t-PA.

DETDESC:

DETD(32)

The results of both chromogenic assays therefore suggest that **CD2** recognizes an epitope on t-PA at or near the catalytic site while DB10 recognizes one somewhat removed from this site. The other **antibodies** in this panel appear to bind at epitopes remote from the active site.

DETDESC:

DETD(36)

To examine the effects of the **antibodies** on the t-PA-PAI-1 interaction, we utilized a monoclonal **antibody** to capture PAI on microtitre wells. This particular **antibody**, which is directed to a region on the PAI-1 not involved in its binding to t-PA, was utilized to minimize. . . the PAI directly on the plastic wells. The ability of [.sup.125 I]t-PA, either free or complexed with the t-PA monoclonal **antibodies**, to bind to the PAI captured on microtitre wells was then examined; results are presented in Table 1. The pattern of the **antibody** effects on this interaction was similar to that observed in the functional assays, with **CD2** pretreatment resulting in the greatest inhibition followed by DB10. Addition of large concentrations of unlabeled t-PA or urokinase resulted in. . . PAI-1 to bind both these proteins. Negligible binding of [.sup.125 I]t-PA was observed in wells coated with only the monoclonal **antibody** to PAI-1.

DETDESC:

DETD(37)

TABLE 1

Effect of Monoclonal **Antibodies** on the Binding of t-PA to PAI-1

[.sup.125 I]t-PA, pretreated for 1 h at 37.degree. C. with the different **antibodies**, was evaluated for its ability to bind PAI-1 captured on microtitre wells.

Data is expressed as % binding relative to. . . the value observed with [.sup.125 I]t-PA which was incubated for 1 h at 37.degree. C. but in the absence of **antibody**. Unlabeled t-PA and urokinase were included at concentrations of 5 .mu.g in the control wells. Each value represents the mean from triplicate wells, .+-. S.D.

Antibody	% Binding
AE5	86 .+-. 9
BA10	91 .+-. 2
CD2	9 .+-. 1
DB10	35 .+-. 4
EG2	70 .+-. 2
MOPC-21	100 .+-. 8
t-PA. . .	

US PAT NO: 5,185,250 [IMAGE AVAILABLE] L5: 19 of 23

DETDESC:

DETD(47)

In one embodiment, the monoclonal antibodies may be human monoclonal antibodies or **chimeric** human-mouse (or other species) monoclonal antibodies. Human monoclonal antibodies may be made by any of numerous techniques known in the. . . Proc. Natl. Acad. Sci. U.S.A. 80:7308-7312; Kozbor et al., 1983, Immunology Today 4:72-79; Olsson et al., 1982, Meth. Enzymol, 92:3-16). **Chimeric** antibody molecules may be prepared containing a mouse (or rat, or other species) antigen-binding domain with human constant regions (Morrison. . .

DETDESC:

DETD(352)

TABLE IV

MONOCLONAL **ANTIBODIES** USED FOR PHENOTYPING

	1/25	3/25	4/4	4/7	4/29	5/1	6/30	6/25
pnTh	(2 mo.)	(8 mo.). . .			(7 mo.)	(2 mo.)	(11 mo.)	(4 yrs.)
CD45	100%	100%						
CD7	--	--			--		60%	
CD2	100	100				100%		100
CD5	100d	--			100d		100	
CD1	--	--					--	
CD4	--	--			--	--	--	
CD8. . .								

US PAT NO: 5,165,923 [IMAGE AVAILABLE] L5: 20 of 23

SUMMARY:

BSUM(30)

The . . . of human, murine, monkey, rat, hamster, chicken or even rabbit origin. The invention therefore contemplates the use of human antibodies, "**humanized**" or chimaeric antibodies from mouse, rat, or other species, bearing human constant and/or variable region domains, single domain antibodies (e.g.,. . .

DETDESC:

DETD(98)

HRS-3, . . . of HRS-1, also yielded a relatively ineffective immunotoxin. Thus, it can be deduced that the affinity (avidity) of the CD30 **antibodies** rather than the epitope they recognize is the primary determinant of their potency as ricin A containing immunotoxins. Different conclusions about the importance of epitope location have been drawn from other studies. Shen et al. (43) concluded that both **antibody** affinity and epitope location determined the potency of CD22 immunotoxins. By contrast, Press et al. (44), in a study of three **CD2** immunotoxins, concluded that epitope location critically influenced immunotoxin potency: immunotoxins recognizing one epitope on the **CD2** molecule were rapidly transported to lysosomes and degraded, whereas an immunotoxin recognizing another epitope lying closer to the membrane remained. . .
=>

```
?begin 55,72,154,399,351

      27oct96 10:06:33 User208760 Session B22.1
            $0.09    0.003 Hrs File1
     $0.09  Estimated cost File1
     $0.09  Estimated cost this search
     $0.09  Estimated total session cost   0.003 Hrs.

SYSTEM:OS  - DIALOG OneSearch
  File  55:BIOSIS PREVIEWS(R)  1985-1996/Oct W3
         (c) 1996 BIOSIS
  File  72:EMBASE  1985-1996/Iss 42
         (c) 1996 Elsevier Science B.V.
  File 154:MEDLINE(R)  1985-1996/Dec W3
         (c) format only 1996 Knight-Ridder Info
*File 154: Type HELP NEWS 154 for 1996 reload information.
***  MEDLINE updates delayed. See HELP DELAY 154.
  File 399:CA SEARCH(R)  1967-1996/UD=12518
         (c) 1996 American Chemical Society
*File 399: Use is subject to the terms of your user/customer agreement.
For format prices, including formats 6 & 8, see HELP RATES 399.
  File 351:DERWENT WPI  1981-1996/UD=9642;UA=9638;UM=9631
         (c)1996 Derwent Info Ltd

      Set  Items  Description
      ---  -----  -----------
?e au=bazin


Ref    Items  Index-term
E1         2  AU=BAZILYUK, OLGA V.
E2         8  AU=BAZILYUK, T. N.
E3         1 *AU=BAZIN
E4        41  AU=BAZIN A
E5         1  AU=BAZIN A A
E6         2  AU=BAZIN A L
E7         1  AU=BAZIN A R
E8        20  AU=BAZIN A.
E9         2  AU=BAZIN A.R.
E10        3  AU=BAZIN AR
E11       28  AU=BAZIN B
E12        1  AU=BAZIN B H

          Enter P or PAGE for more
?p


Ref    Items  Index-term
E13       11  AU=BAZIN B.
E14        1  AU=BAZIN BH
E15       96  AU=BAZIN C
E16       50  AU=BAZIN C.
E17        1  AU=BAZIN D
E18        2  AU=BAZIN E
E19       13  AU=BAZIN E T
E20        4  AU=BAZIN E.
E21        2  AU=BAZIN F
E22        1  AU=BAZIN F C H
```

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E23         1  AU=BAZIN F.
E24         6  AU=BAZIN G

           Enter P or PAGE for more
?p


Ref    Items  Index-term
E25        1  AU=BAZIN G L
E26        3  AU=BAZIN G.
E27      332  AU=BAZIN H
E28      126  AU=BAZIN H.
E29        2  AU=BAZIN J
E30        2  AU=BAZIN J C L
E31       11  AU=BAZIN J E
E32       15  AU=BAZIN J P
E33        1  AU=BAZIN J.
E34        4  AU=BAZIN J.-E.
E35        6  AU=BAZIN J.-P.
E36        4  AU=BAZIN J.C.

           Enter P or PAGE for more
?s e27,e28

             332  AU=BAZIN H
             126  AU=BAZIN H.
      S1     458  E27,E28
?s s1 and cd2

             458  S1
           14716  CD2
      S2      12  S1 AND CD2
?rd s12

>>>Set 12 has not yet been created.
?rd s2

>>>Duplicate detection is not supported for File 351.

>>>Records from unsupported files will be retained in the RD set.
...completed examining records
      S3       9  RD S2 (unique items)
?t s3/3/all


 3/3/1     (Item 1 from file: 55)
DIALOG(R)File  55:BIOSIS PREVIEWS(R)
(c) 1996 BIOSIS. All rts. reserv.

13135772     BIOSIS Number: 99135772
  An anti-CD2 mAb induces immunosuppression and hyporesponsiveness of CD2+
human T cells in vitro
  Latinne D; De La Parra B; Nizet Y; Cornet A; Giovino-Barry V; Monroy R L;
White-Scharf M E; Bazin H
  Transplantation Immunol., Univ. Louvain Med. Sch., Clos Chapelle aux
Champs 30, B-1200 Brussels, Belgium
  International Immunology 8 (7). 1996.  1113-1119.
  Full Journal Title:  International Immunology
```

ISSN: 0953-8178
Language: ENGLISH
Print Number: Biological Abstracts Vol. 102 Iss. 006 Ref. 083903

3/3/2 (Item 2 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

13031624 BIOSIS Number: 99031624
Anti-CD2 monoclonal antibody elicits specific alloantigen hyporesponsiveness
Schad V; Maher M; Kolber D; Giovino-Barry V; Leguern A; Xu Y; White-Scharf M E; Bazin H; Latinne D
BioTransplant Inc., Charlestown, MA, USA
FASEB Journal 10 (6). 1996. A1313.
Full Journal Title: Joint Meeting of the American Society for Biochemistry and Molecular Biology, the American Society for Investigative Pathology and the American Association of Immunologists, New Orleans, Louisiana, USA, June 2-6, 1996. FASEB Journal
ISSN: 0892-6638
Language: ENGLISH
Document Type: CONFERENCE PAPER
Print Number: Biological Abstracts/RRM Vol. 048 Iss. 007 Ref. 125360

3/3/3 (Item 3 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

13031623 BIOSIS Number: 99031623
T cell responsiveness to alloantigen is maintained in SCID mice reconstituted with human splenocytes and is inhibited by an anti-CD2 monoclonal antibody
Buckley M; Brady D; Schad V; Latinne D; Bazin H
BioTransplant Inc., Charlestown, MA, USA
FASEB Journal 10 (6). 1996. A1313.
Full Journal Title: Joint Meeting of the American Society for Biochemistry and Molecular Biology, the American Society for Investigative Pathology and the American Association of Immunologists, New Orleans, Louisiana, USA, June 2-6, 1996. FASEB Journal
ISSN: 0892-6638
Language: ENGLISH
Document Type: CONFERENCE PAPER
Print Number: Biological Abstracts/RRM Vol. 048 Iss. 007 Ref. 125359

3/3/4 (Item 4 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

11810076 BIOSIS Number: 98410076
A rat monoclonal anti-(human CD2) and L-leucine methyl ester impacts on human-SCID mouse graft and B lymphoproliferative syndrome
Bombil F; Kints J P; Havaux X; Scheiff J M; Bazin H; Latinne D
Experimental Immunol. Unit, Univ. Louvain, Clos chapelle-aux-champs 30-56, Brussels 1200, Belgium
Cancer Immunology Immunotherapy 40 (6). 1995. 383-389.

Full Journal Title: Cancer Immunology Immunotherapy
ISSN: 0340-7004
Language: ENGLISH
Print Number: Biological Abstracts Vol. 100 Iss. 006 Ref. 087668

3/3/5 (Item 5 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

11607416 BIOSIS Number: 98207416
Perturbation of CD2 can induce alloantigen specific hyporesponsiveness in naive T cells
Giovino-Barry V C; Latinne D; Xu Y; Glaser R M; Dickerson W M; Matejic T; Schacter B Z; Greenstein J L; Bazin H; White-Scharf M E; Monroy R L
BioTransplant Inc., Boston, MA 02129, USA
FASEB Journal 9 (3). 1995. A232.
Full Journal Title: Experimental Biology 95, Part I, Atlanta, Georgia, USA, April 9-13, 1995. FASEB Journal
ISSN: 0892-6638
Language: ENGLISH
Document Type: CONFERENCE PAPER
Print Number: Biological Abstracts/RRM Vol. 047 Iss. 005 Ref. 081079

3/3/6 (Item 6 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

9337062 BIOSIS Number: 43082062
INHIBITION OF T-CELL ACTIVATION BY LO-CD2-A A RAT MONOCLONAL ANTIBODY AGAINST THE HUMAN CD2 GLYCOPROTEIN
DE LA PARRA B; VAN DEN BRANDEN K; SMYEJ I; BAZIN H
UNIV. CATHOL. LOUVAIN, LOUVAIN-LA-NEUVE, BELG.
SECOND BELGIAN CONGRESS OF ZOOLOGY, DIEPENBEEK, BELGIUM, NOVEMBER 15-16, 1991. BELG J ZOOL 121 (SUPPL. 1). 1991. 13. CODEN: BJZOE
Language: ENGLISH
Document Type: CONFERENCE PAPER

3/3/7 (Item 1 from file: 72)
DIALOG(R)File 72:EMBASE

10072540 EMBASE No: 96260773
An anti-CD2 monoclonal antibody that elicits alloantigen-specific hyporesponsiveness
Schad V.; Greenstein J.L.; Giovino-Barry V.; LeGuern A.; Matejic T.; Glaser R.; Dickerson M.; Xu Y.; Bazin H.; Latinne D.; Monroy R.; White-Scharf M.E.
BioTransplant Inc, Charlestown Navy Yard, Building 75, 3rd Avenue, Charlestown, MA 02129 USA
Transplantation Proceedings (USA) , 1996, 28/4 (2051-2053) CODEN: TRPPA
ISSN: 0041-1345
LANGUAGES: English

3/3/8 (Item 2 from file: 72)

DIALOG(R)File 72:EMBASE
(c) 1996 Elsevier Science B.V. All rts. reserv.

9657843 EMBASE No: 95208029
A rat monoclonal anti-(human CD2) and L-leucine methyl ester impacts an human/SCID mouse graft and B lymphoproliferative syndrome
Bombil F.; Kints J.P.; Havaux X.; Scheiff J.M.; Bazin H.; Latinne D.
Experimental Immunology Unit, University of Louvain, Clos chapelle-aux-champs 30-56, Brussels 1200 Belgium
Cancer Immunology Immunotherapy (Germany) , 1995, 40/6 (383-389) CODEN: CIIMD ISSN: 0340-7004
LANGUAGES: English SUMMARY LANGUAGES: English

3/3/9 (Item 1 from file: 351)
DIALOG(R)File 351:DERWENT WPI
(c)1996 Derwent Info Ltd. All rts. reserv.

010035313 WPI Acc No: 94-303026/37
XRAM Acc No: C94-138226
New anti-CD2 monocolonal antibody - used for inhibiting an immune response mdiated by T cell activation and proliferation
Patent Assignee: (UYLO-) UNIV CATHOLIQUE LOUVAIN
Author (Inventor): BAZIN H; LATINNE D
Patent Family:

CC	Number	Kind	Date	Week	
WO	9420619	A1	940915	9437	(Basic)
AU	9462181	A	940926	9503	
EP	687300	A1	951220	9604	

Priority Data (CC No Date): US 119032 (930909); US 27008 (930305)
Applications (CC,No,Date): EP 94909270 (940304); WO 94IB43 (940304); WO 94IB43 (940304); AU 9462181 (940304)
?t s3/7/1

3/7/1 (Item 1 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)
(c) 1996 BIOSIS. All rts. reserv.

13135772 BIOSIS Number: 99135772
An anti-CD2 mAb induces immunosuppression and hyporesponsiveness of CD2+ human T cells in vitro
Latinne D; De La Parra B; Nizet Y; Cornet A; Giovino-Barry V; Monroy R L; White-Scharf M E; Bazin H
Transplantation Immunol., Univ. Louvain Med. Sch., Clos Chapelle aux Champs 30, B-1200 Brussels, Belgium
International Immunology 8 (7). 1996. 1113-1119.
Full Journal Title: International Immunology
ISSN: 0953-8178
Language: ENGLISH
Print Number: Biological Abstracts Vol. 102 Iss. 006 Ref. 083903
We describe here the potent specific immunosuppression obtained in vitro by LO-CD2a, a rat mAb directed against the human CD2 molecule. Addition of low dose LO-CD2a (40 ng/ml) at the time of mixed lymphocyte culture (MLC) initiation inhibits 80% of the proliferation and, more impressive, addition of the mAb 4 days after culture initiation at a similar concentration still suppresses 50% of the MLC. When responder T cells previously treated with

LO-CD2a are challenged a second time by the same donor or third party allogeneic cells, hyporesponsiveness occurs in both cases, although reactivity to T cell mitogenic stimulation persists. Finally, the low production of cytokines such as tumor necrosis factor-alpha and IFN-gamma after incubation of human T cells with LO-CD2a suggests the absence of T cell activation. These results demonstrate that LO-CD2a mAb has a significant immunosuppressive effect and induces hyporesponsiveness in vitro, thereby suggesting potential efficacy in vivo for the treatment of acute rejection and for the induction of tolerance in allotransplantation.
?s cd2 and antibod? and (humanis? or humaniz? or chimeric)

```
          14716  CD2
         906426  ANTIBOD?
           1631  HUMANIS?
           1681  HUMANIZ?
          29172  CHIMERIC
      S4     57  CD2 AND ANTIBOD? AND (HUMANIS? OR HUMANIZ? OR CHIMERIC)
?rd s4

>>>Duplicate detection is not supported for File 351.

>>>Records from unsupported files will be retained in the RD set.
...examined 50 records  (50)
...completed examining records
      S5     34  RD S4 (unique items)
?t s5/3/all


 5/3/1     (Item 1 from file: 55)
DIALOG(R)File  55:BIOSIS PREVIEWS(R)
(c) 1996 BIOSIS. All rts. reserv.

12149094     BIOSIS Number: 98749094
  Emergence of CD52-, glycosylphosphatidylinositol-anchor-deficient
lymphocytes in rheumatoid arthritis patients following Campath-1H treatment
  Brett S J; Baxter G; Cooper H; Rowan W; Regan T; Tite J; Rapson N
  Molecular Immunology Group, Wellcome Research Laboratories, Beckenham,
Kent BR3 3BS, UK
  International Immunology 8 (3). 1996.  325-334.
  Full Journal Title:  International Immunology
  ISSN: 0953-8178
  Language: ENGLISH
  Print Number: Biological Abstracts Vol. 101 Iss. 009 Ref. 133369


 5/3/2     (Item 2 from file: 55)
DIALOG(R)File  55:BIOSIS PREVIEWS(R)
(c) 1996 BIOSIS. All rts. reserv.

12033429     BIOSIS Number: 98633429
  A sensitive assay for detecting low-affinity additional ligands for the
adhesion pair rat CD2 and CD48
  Brown M H; Preston S; Barclay A N
  MRC Cellular Immunol. Unit, Sir William Dunn Sch. Pathol., Oxford OX1
3RE, UK
  European Journal of Immunology 25 (12). 1995.  3222-3228.
  Full Journal Title:  European Journal of Immunology
  ISSN: 0014-2980
```

Language: ENGLISH
Print Number: Biological Abstracts Vol. 101 Iss. 004 Ref. 049174

5/3/3 (Item 3 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

11950129 BIOSIS Number: 98550129
CD2 expression in acute promyelocytic leukemia is associated with microgranular morphology (FAB M3v) but not with any PML gene breakpoint
Biondi A; Luciano A; Bassan R; Mininni D; Specchia G; Lanzi E; Castagna S ; Cantu-Rajnoldi A; Liso V; Masera G; Barbui T; Rambaldi A
Clinica Pediatrica Universita di Milano, Ospedale San Gerardo, Via Donizetti 106, 20052 Monza, Italy
Leukemia (Basingstoke) 9 (9). 1995. 1461-1466.
Full Journal Title: Leukemia (Basingstoke)
ISSN: 0887-6924
Language: ENGLISH
Print Number: Biological Abstracts Vol. 100 Iss. 012 Ref. 186820

5/3/4 (Item 4 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

11664438 BIOSIS Number: 98264438
Mammalian CD2 is an effective heterologous marker of the cell surface in Drosophila
Dunin-Borkowski O M; Brown N H
Wellcome/CRC Inst., Tennis Court Road, Cambridge CB2 1QR, UK
Developmental Biology 168 (2). 1995. 689-693.
Full Journal Title: Developmental Biology
ISSN: 0012-1606
Language: ENGLISH
Print Number: Biological Abstracts Vol. 099 Iss. 012 Ref. 169356

5/3/5 (Item 5 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

11540178 BIOSIS Number: 98140178
Cross-linking of the CAMPATH-1 antigen (CD52) triggers activation of normal human T lymphocytes
Rowan W C; Hale G; Tite J P; Brett S J
Molecular Immunology Section, Wellcome Res. Lab., Beckenham, Kent BR3 3BS, UK
International Immunology 7 (1). 1995. 69-77.
Full Journal Title: International Immunology
ISSN: 0953-8178
Language: ENGLISH
Print Number: Biological Abstracts Vol. 099 Iss. 007 Ref. 096735

5/3/6 (Item 6 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

11249543 BIOSIS Number: 97449543
Human high-affinity Fc IgG receptor (Fc-gamma-RI)-mediated phagocytosis and pinocytosis in COS cells
Socolovsky M; Hockaday A R; Allen J M
Physiol. Lab., Univ. Cambridge, Downing St., Cambridge CB2 3EG/UK
European Journal of Cell Biology 64 (1). 1994. 29-44.
Full Journal Title: European Journal of Cell Biology
ISSN: 0171-9335
Language: ENGLISH
Print Number: Biological Abstracts Vol. 098 Iss. 008 Ref. 103855

5/3/7 (Item 7 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)
(c) 1996 BIOSIS. All rts. reserv.

10465064 BIOSIS Number: 96065064
REGULATION OF HIV PRODUCTION BY BLOOD MONONUCLEAR CELLS FROM HIV-INFECTED DONORS II. HIV-1 PRODUCTION DEPENDS ON T CELL-MONOCYTE INTERACTION
DIEGEL M L; MORAN P A; GILLILAND L K; DAMLE N K; HAYDEN M S; ZARLING J M; LEDBETTER J A
BRISTOL-MYERS SQUIBB PHARMACEUTICAL RES. INST., 3005 FIRST AVE., SEATTLE, WA 98121, USA.
AIDS RES HUM RETROVIRUSES 9 (5). 1993. 465-473. CODEN: ARHRE
Full Journal Title: Aids Research and Human Retroviruses
Language: ENGLISH

5/3/8 (Item 8 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)
(c) 1996 BIOSIS. All rts. reserv.

10429041 BIOSIS Number: 96029041
THE NH-2-TERMINAL DOMAIN OF THE RAT CD2 BINDS RAT CD48 WITH A LOW AFFINITY AND BINDING DOES NOT REQUIRE GLYCOSYLATION OF CD2
VAN DER MERWE P A; MCPHERSON D C; BROWN M H; BARCLAY A N; CYSTER J G; WILLIAMS A F; DAVIS S J
MRC CELL. IMMUNOL. UNIT, SIR WILLIAM DUNN SCH. PATHOL., UNIV. OXFORD, SOUTH PARKS RD., OXFORD OX1 3RE, UK.
EUR J IMMUNOL 23 (6). 1993. 1373-1377. CODEN: EJIMA
Full Journal Title: European Journal of Immunology
Language: ENGLISH

5/3/9 (Item 9 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)
(c) 1996 BIOSIS. All rts. reserv.

10424725 BIOSIS Number: 96024725
IDENTIFICATION OF THE T CELL SURFACE SIGNAL-TRANSDUCING GLYCOPROTEIN SGP-60 AS CD8 A COUNTER-RECEPTOR FOR MOUSE CD2
KATO K; TAMURA N; OKUMURA K; YAGITA H
DEP. IMMUNOL., JUNTENDO UNIV. SCH. MED., 2-1-1 HONGO, BUNKYO-KU, TOKYO 113, JPN.
EUR J IMMUNOL 23 (6). 1993. 1412-1415. CODEN: EJIMA
Full Journal Title: European Journal of Immunology
Language: ENGLISH

5/3/10 (Item 10 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

10028068 BIOSIS Number: 95028068
CD48 IS A COUNTER-RECEPTOR FOR MOUSE CD2 AND IS INVOLVED IN T CELL ACTIVATION
KATO K; KOYANAGI M; OKADA H; TAKANASHI T; WONG Y W; WILLIAMS A F; OKUMURA K; YAGITA H
DEP. IMMUNOL., JUNTENDO UNIV. SCH. MED., 2-1-1 HONGO, BUNKYO-KU, TOKYO 113, JPN.
J EXP MED 176 (5). 1992. 1241-1249. CODEN: JEMEA
Full Journal Title: Journal of Experimental Medicine
Language: ENGLISH

5/3/11 (Item 11 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

9568780 BIOSIS Number: 94073780
THE CD3-ZETA CYTOPLASMIC DOMAIN MEDIATES CD2-INDUCED T CELL ACTIVATION
HOWARD F D; MOINGEON P; MOEBIUS U; MCCONKEY D J; YANDAVA B; GENNERT T E; REINHERZ E L
DANA-FARBER CANCER INST., 44 BINNEY STREET, BOSTON, MASS. 02115.
J EXP MED 176 (1). 1992. 139-145. CODEN: JEMEA
Full Journal Title: Journal of Experimental Medicine
Language: ENGLISH

5/3/12 (Item 12 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

9117105 BIOSIS Number: 93102105
ANTIBODY-TARGETED INTERLEUKIN 2 STIMULATES T-CELL KILLING OF AUTOLOGOUS TUMOR CELLS
GILLIES S D; REILLY E B; LO K-M; REISFELD R A
DEP. IMMUNOL., SCRIPPS RES. INST., 10666 NORTH TORREY PINES ROAD, LA JOLLA, CALIF. 92037, USA.
PROC NATL ACAD SCI U S A 89 (4). 1992. 1428-1432. CODEN: PNASA
Full Journal Title: Proceedings of the National Academy of Sciences of the United States of America
Language: ENGLISH

5/3/13 (Item 13 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

7633815 BIOSIS Number: 90001815
ANTIBODY-INDUCED MITOGENICITY MEDIATED BY A CHIMERIC CD2-C-FMS RECEPTOR
ROUSSEL M F; TRANSY C; KATO J-Y; REINHERZ E L; SHERR C J
DEP. TUMOR. CELL BIOL., ST. JUDE CHILD. RES. HOSP., MEMPHIS, TENN. 38105.
MOL CELL BIOL 10 (5). 1990. 2407-2412. CODEN: MCEBD
Full Journal Title: Molecular and Cellular Biology

Language: ENGLISH

5/3/14 (Item 14 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

7594255 BIOSIS Number: 39106862
A CHIMERIC RECEPTOR COMPOSED OF THE EXTRACELLULAR DOMAIN OF CD2 AND THE TYROSINE KINASE DOMAIN OF THE CSF-1 RECEPTOR FMS ENABLES NIH-3T3 CELLS TO RESPOND MITOGENICALLY TO CD2 ANTIBODIES
ROUSSEL M F; TRANSY C; KATO J-Y; REINHERZ E; SHERR C J
DEP. TUMOR CELL BIOL., HARV. MED. SCH., BOSTON, MASS. 02115.
SYMPOSIUM ON SIGNAL TRANSDUCTION AND GENE ACTIVATION IN DEVELOPMENT HELD AT THE 19TH ANNUAL UCLA (UNIVERSITY OF CALIFORNIA-LOS ANGELES) SYMPOSIA ON MOLECULAR AND CELLULAR BIOLOGY, STEAMBOAT SPRINGS, COLORADO, USA, MARCH 31-APRIL 7, 1990. J CELL BIOCHEM SUPPL 0 (14 PART E). 1990. 167. CODEN: JCBSD
Language: ENGLISH
Document Type: CONFERENCE PAPER

5/3/15 (Item 1 from file: 72)
DIALOG(R)File 72:EMBASE

9826713 EMBASE No: 96008399
A sensitive assay for detecting low-affinity interactions at the cell surface reveals no additional ligands for the adhesion pair rat CD2 and CD48
Brown M.H.; Preston S.; Barclay A.N.
MRC Cellular Immunology Unit, Sir William Dunn School of Pathology, Oxford OX1 3RE United Kingdom
European Journal of Immunology (Germany) , 1995, 25/12 (3222-3228) CODEN: EJIMA ISSN: 0014-2980
LANGUAGES: English SUMMARY LANGUAGES: English

5/3/16 (Item 2 from file: 72)
DIALOG(R)File 72:EMBASE

9677442 EMBASE No: 95222616
Molecular analyses of the association of CD4 with two members of the transmembrane 4 superfamily, CD81 and CD82
Imai T.; Kakizaki M.; Nishimura M.; Yoshie O.
Shionogi Inst. for Medical Sciences, 2-5-1 Mishima, Settsu-shi, Osaka 566 Japan
Journal of Immunology (USA) , 1995, 155/3 (1229-1239) CODEN: JOIMA ISSN: 0022-1767
LANGUAGES: English SUMMARY LANGUAGES: English

5/3/17 (Item 3 from file: 72)
DIALOG(R)File 72:EMBASE

9237781 EMBASE No: 94189280

Eosinophil adhesion to nasal polyp endothelium is P-selectin-dependent
Symon F.A.; Walsh G.M.; Watson S.R.; Wardlaw A.J.
Department of Respiratory Medicine, Glenfield Hospital, Leicester LE3 9QP United Kingdom
J. EXP. MED. (USA) , 1994, 180/1 (371-376) CODEN: JEMEA ISSN: 0022-1007
LANGUAGES: English SUMMARY LANGUAGES: English

5/3/18 (Item 4 from file: 72)
DIALOG(R)File 72:EMBASE

9164650 EMBASE No: 94117991
Expression of immunoglobulin and scavenger receptor superfamily domains as chimeric proteins with domains 3 and 4 of CD4 for ligand analysis
Brown M.H.; Barclay A.N.
MRC Cellular Immunology Unit, Sir William Dunn School of Pathology, Oxford OX1 3RE United Kingdom
PROTEIN ENG. (United Kingdom) , 1994, 7/4 (515-521) CODEN: PRENE ISSN: 0269-2139
LANGUAGES: English SUMMARY LANGUAGES: English

5/3/19 (Item 5 from file: 72)
DIALOG(R)File 72:EMBASE

8861856 EMBASE No: 93165729
Identification of the T cell surface signal-transducing glycoprotein sgp-60 as CD48, a counter-receptor for mouse CD2
Kato K.; Tamura N.; Okumura K.; Yagita H.
Department of Immunology, Juntendo University School Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113 Japan
EUR. J. IMMUNOL. (Germany) , 1993, 23/6 (1412-1415) CODEN: EJIMA ISSN: 0014-2980
LANGUAGES: English SUMMARY LANGUAGES: English

5/3/20 (Item 6 from file: 72)
DIALOG(R)File 72:EMBASE

8422959 EMBASE No: 92099056
Differential costimulatory effects of adhesion molecules B7, ICAM-1, LFA-3, and VCAM-1 on resting and antigen-primed CD4+ T lymphocytes
Damle N.K.; Klussman K.; Linsley P.S.; Aruffo A.
Bristol-Myers Squibb Pharmaceutical Research Institute, 3005 First Avenue, Seattle, WA 98121 USA
J. IMMUNOL. (USA) , 1992, 148/7 (1985-1992) CODEN: JOIMA ISSN: 0022-1767
LANGUAGES: English SUMMARY LANGUAGES: English

5/3/21 (Item 1 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

09625619 96147219
The epithelial mucin MUC1 contains at least two discrete signals specifying membrane localization in cells.
Pemberton LF; Rughetti A; Taylor-Papadimitriou J; Gendler SJ
Imperial Cancer Research Fund, London, United Kingdom.
J Biol Chem (UNITED STATES) Jan 26 1996, 271 (4) p2332-40, ISSN 0021-9258 Journal Code: HIV
Contract/Grant No.: R01-CA64389, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE

5/3/22 (Item 2 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

09387800 95317800
Functional significance of CD23- on CD23-transfected Th2 clone.
Nambu M; Hagen M; Sandor M; Sacco RE; Kwack K; Lynch RG
Department of Pathology, College of Medicine, University of Iowa, Iowa City 52242, USA.
Immunol Lett (NETHERLANDS) Jan 1995, 44 (2-3) p163-7, ISSN 0165-2478 Journal Code: GIH
Contract/Grant No.: R01-CA-49228, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE

5/3/23 (Item 3 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

09086284 95016284
Coengagement of CD2 with LFA-1 or VLA-4 by bispecific ligand fusion proteins primes T cells to respond more effectively to T cell receptor-dependent signals.
Dietsch MT; Chan PY; Kanner SB; Gilliland LK; Ledbetter JA; Linsley PS; Aruffo A
Bristol-Myers Squibb Pharmaceutical Research Institute, Seattle, Washington 98121.
J Leukoc Biol (UNITED STATES) Oct 1994, 56 (4) p444-52, ISSN 0741-5400 Journal Code: IWY
Languages: ENGLISH
Document type: JOURNAL ARTICLE

5/3/24 (Item 4 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

08855347 94170347
Specificity and function of monoclonal antibodies directed against Ewing sarcoma cells.
Shi LR; Eichelbauer D; Borchard F; Jurgens H; Gobel U; Schneider EM
Immunology Laboratory, Institute of Blood Coagulation and Transfusion Medicine, University of Dusseldorf, Germany.
Cancer Immunol Immunother (GERMANY) Mar 1994, 38 (3) p208-13, ISSN 0340-7004 Journal Code: CN3

Languages: ENGLISH
Document type: JOURNAL ARTICLE

5/3/25 (Item 5 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

08770368 94085368
Affinity and kinetic analysis of the interaction of the cell adhesion molecules rat CD2 and CD48.
van der Merwe PA; Brown MH; Davis SJ; Barclay AN
MRC Cellular Immunology Unit, Sir William Dunn School of Pathology, University of Oxford, UK.
EMBO J (ENGLAND) Dec 15 1993, 12 (13) p4945-54, ISSN 0261-4189
Journal Code: EMB
Languages: ENGLISH
Document type: JOURNAL ARTICLE

5/3/26 (Item 1 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

122029803 CA: 122(3)29803n PATENT
An antibody to a T-cell epitope for inhibition of T-cell activation and proliferation in the control of transplant rejection and autoimmune disease
INVENTOR(AUTHOR): Bazin, Herve; Latinne, Dominique
LOCATION: Belg.
ASSIGNEE: Universite Catholique de Louvain
PATENT: PCT International ; WO 9420619 A1 DATE: 940915
APPLICATION: WO 94IB43 (940304) *US 27008 (930305) *US 119032 (930909)
PAGES: 101 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: C12N-015/13A; C12P-021/08B; A61K-039/395 DESIGNATED COUNTRIES: AU; CA; FI; JP; KR; NO; NZ; US DESIGNATED REGIONAL: AT; BE; CH; DE; DK; ES; FR; GB; GR; IE; IT; LU ; MC; NL; PT; SE

5/3/27 (Item 2 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

119224262 CA: 119(21)224262a PATENT
Recombinant monkey and monkey-human antibodies for human therapy
INVENTOR(AUTHOR): Newman, Roland A.; Hanna, Nabil; Raab, Ronald W.
LOCATION: USA
ASSIGNEE: IDEC Pharmaceuticals Corp.
PATENT: PCT International ; WO 9302108 A1 DATE: 930204
APPLICATION: WO 92US6194 (920724) *US 735064 (910725) *US 856281 (920323)
PAGES: 91 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: C07K-015/28A; C07H-015/00B; C12P-021/08B; C12N-005/26B; C12N-015/02B
DESIGNATED COUNTRIES: AT; AU; BB; BG; BR; CA; CH; CS; DE; DK; ES; FI; GB; HU; JP; KP; KR; LK; LU; MG; MN; MW; NL; NO; PL; RO; RU; SD; SE; US
DESIGNATED REGIONAL: AT; BE; CH; DE; DK; ES; FR; GB; GR; IT; LU; MC; NL; SE; BF; BJ; CF; CG; CI; CM; GA; GN; ML; MR; SN; TD; TG

5/3/28 (Item 3 from file: 399)

DIALOG(R)File 399:CA SEARCH(R)
(c) 1996 American Chemical Society. All rts. reserv.

119158236 CA: 119(15)158236s PATENT
CDR-grafted humanized chimeric T-cell antibody
INVENTOR(AUTHOR): Waldmann, Herman; Walsh, Louise; Crowe, James Scott; Lewis, Alan Peter
LOCATION: UK,
ASSIGNEE: Wellcome Foundation Ltd.
PATENT: PCT International ; WO 9311237 A1 DATE: 930610
APPLICATION: WO 92GB2251 (921204) *GB 9125979 (911206)
PAGES: 49 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: C12N-015/13A; C12N-015/62B; C12P-021/08B; A61K-039/395B; C12N-005/10B; C07K-015/28B
DESIGNATED COUNTRIES: JP; US DESIGNATED REGIONAL: AT; BE; CH; DE; DK; ES ; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE

5/3/29 (Item 4 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
(c) 1996 American Chemical Society. All rts. reserv.

118146079 CA: 118(15)146079j PATENT
The CD2-binding domain of lymphocyte function-associated antigen 3
INVENTOR(AUTHOR): Wallner, Barbara P.; Miller, Glenn T.; Rosa, Margaret D.
LOCATION: USA
ASSIGNEE: Biogen, Inc.
PATENT: European Pat. Appl. ; EP 503648 A1 DATE: 920916
APPLICATION: EP 92104320 (920312) *US 667971 (910312) *US 770967 (911007)
PAGES: 85 pp. CODEN: EPXXDW LANGUAGE: English CLASS: C12N-015/12A; C12N-015/62B; C07K-013/00B; C12N-001/21B; G01N-033/564B; G01N-033/566B; A61K-037/02B; A61K-039/395B DESIGNATED COUNTRIES: AT; BE; CH; DE; DK; ES; FR; GB; GR; IT; LI; LU; MC; NL; PT; SE

5/3/30 (Item 5 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
(c) 1996 American Chemical Society. All rts. reserv.

117210649 CA: 117(21)210649d PATENT
B-cell B7 antigen as ligand for CD28 antigen and methods for regulating functional T-cell responses, etc.
INVENTOR(AUTHOR): Linsley, Peter S.; Ledbetter, Jeffrey A.; Damle, Nitin K.; Brady, William
LOCATION: USA
ASSIGNEE: Bristol-Myers Squibb Co.
PATENT: PCT International ; WO 9200092 A1 DATE: 920109
APPLICATION: WO 91US4682 (910701) *US 547980 (900702) *US 722101 (910627)
PAGES: 106 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: A61K-037/02A
DESIGNATED COUNTRIES: CA; JP DESIGNATED REGIONAL: AT; BE; CH; DE; DK; ES ; FR; GB; GR; IT; LU; NL; SE

5/3/31 (Item 1 from file: 351)
DIALOG(R)File 351:DERWENT WPI
(c)1996 Derwent Info Ltd. All rts. reserv.

010099678 WPI Acc No: 95-000931/01

XRAM Acc No: C95-000387
Image available
New monoclonal antibodies specific for CD2 - for inhibiting HIV-1 propagation in infected T cells without affecting immune response to other pathogens
Patent Assignee: (BRIM) BRISTOL-MYERS SQUIBB CO
Author (Inventor): DIEGEL M L; GILLILAND L K; LEDBETTER J A; LINSLEY P S; MORAN P A; ZARLING J M
Patent Family:

CC Number	Kind	Date	Week	
EP 626447	A1	941130	9501	(Basic)
CA 2124126	A	941126	9509	
JP 7147983	A	950613	9532	

Priority Data (CC No Date): US 68946 (930525)
Applications (CC,No,Date): JP 94111160 (940525); EP 94108104 (940525); CA 2124126 (940524)

5/3/32 (Item 2 from file: 351)
DIALOG(R)File 351:DERWENT WPI

009503520 WPI Acc No: 93-197056/24
XRAM Acc No: C93-087362
CDR-grafted humanised chimeric T cell antibodies - inhibit T cell proliferation, for treating T-cell mediated diseases e.g. graft-versus-host disease, auto-immune-diseases etc.
Patent Assignee: (WALD/) WALDMANN H; (WALS/) WALSH L; (WELL) WELLCOME FOUND LTD; (CROW/) CROWE J S; (LEWI/) LEWIS A P
Author (Inventor): CROWE J S; LEWIS A P; WALDMANN H; WALSH L
Patent Family:

CC Number	Kind	Date	Week	
WO 9311237	A1	930610	9324	(Basic)
JP 7504808	W	950601	9530	
EP 667902	A1	950823	9538	
US 5502167	A	960326	9618	

Priority Data (CC No Date): GB 9125979 (911206)
Applications (CC,No,Date): WO 92GB2251 (921204); US 244626 (940715); WO 92GB2251 (921204); WO 92GB2251 (921204); JP 93509972 (921204); EP 92924782 (921204); WO 92GB2251 (921204)

5/3/33 (Item 3 from file: 351)
DIALOG(R)File 351:DERWENT WPI

009352019 WPI Acc No: 93-045499/05
XRAM Acc No: C93-020601
Recombinant vaccinia virus expressing light and/or heavy chains of an antibody - used to produce fragments, chimeric or humanised antibodies, e.g. against tumour cell markers
Patent Assignee: (WELL) WELLCOME FOUND LTD
Author (Inventor): CARROLL A R; CLARKE B E; ROWLANDS D J
Patent Family:

CC Number	Kind	Date	Week	
WO 9301296	A1	930121	9305	(Basic)

Priority Data (CC No Date): GB 9114468 (910704)
Applications (CC,No,Date): WO 92GB1170 (920629)

5/3/34 (Item 4 from file: 351)
DIALOG(R)File 351:DERWENT WPI

009182322 WPI Acc No: 92-309758/38
XRAM Acc No: C92-137555
XRPX Acc No: N92-237113 *Image available*
Monoclonal antibodies active against lymphocyte function associated antigen-3 - for treating inflammation and autoimmune diseases, and for detecting LFA-3 protein in a sample
Patent Assignee: (BIOJ) BIOGEN INC
Author (Inventor): CHISHOLM P L; SATO V L; WALLNER B P
Patent Family:

CC	Number	Kind	Date	Week	
EP	503646	A1	920916	9238	(Basic)
WO	9216563	A1	921001	9242	
AU	9217711	A	921021	9303	

Priority Data (CC No Date): US 667975 (910312)
Applications (CC,No,Date): EP 92104318 (920312); WO 92US2044 (920312); AU 9217711 (920312); WO 92US2044 (920312)
?ds

Set	Items	Description
S1	458	E27,E28
S2	12	S1 AND CD2
S3	9	RD S2 (unique items)
S4	57	CD2 AND ANTIBOD? AND (HUMANIS? OR HUMANIZ? OR CHIMERIC)
S5	34	RD S4 (unique items)

?s s5 and hum5400

34 S5
0 HUM5400
S6 0 S5 AND HUM5400
?s hum5400

S7 0 HUM5400
?